The Health Economics of Haemochromatosis

By

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (Medical Research)

University of Tasmania, Australia

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Declaration of originality

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Statement of co-authorship

This thesis includes papers for which Barbara de Graaff (BdG) is first but not sole author. BdG led the work in developing and conceptualising the papers, implementing the analyses and writing the manuscripts under the primary supervision of Andrew Palmer (AP) and supervisors Amanda Neil (AN), Kristy Sanderson (KS) and Kwang Chien Yee (KY). Throughout the work presented herein she was assisted by co-authors from research alliances. Detailed below are the contributions of BdG and each of her co-authors for each respective paper.

1. The paper reported in Chapter 2:

de Graaff, B. , Neil, A., Sanderson K, Si, L., Yee, K.C. & Palmer AJ. "A Systematic Review and Narrative Synthesis of Health Economic Studies for Hereditary Haemochromatosis" *Applied Health Economics and Health Policy.* October 2015; 13(5): 469-83.

- BdG developed the protocol following Campbell Cochrane Economic Methods Group and the PRISMA Statement. BdG performed the data collection, extraction and narrative synthesis. The analysis was conducted under the supervision of AP and AN. BdG drafted the manuscript and coordinated revisions and submission.
- AP was involved in the initial conceptualization, development and drafting of the protocol, along with interpretation of the results and manuscript revisions.
- AN was involved in conceptualising the paper, interpretation of the results and manuscript revisions.
- KS was involved with conceptualising the paper and manuscript revisions.
- LS assisted with paper screening and manuscript revision.
- KY provided clinical input into the conceptualisation of the review and assisted with manuscript revision.

2. The paper reported in Chapter 3:

de Graaff, B., Neil, A., Sanderson, K., Yee, K.C. & Palmer AJ. "Quality of life utility values for hereditary haemochromatosis in Australia" *Health and Quality of Life Outcomes*. February 2016; 14(31).

- BdG undertook study design, development of the survey, submission for ethical approval, recruitment, data management and analysis. BdG drafted the manuscript and coordinated revisions and submission.

- AP assisted with conceptualisation of the study, study design, survey development, interpretation of data analyses and manuscript revisions.
- AN assisted with survey development, study design, survey development, interpretation of data analyses and manuscript revisions.
- KS assisted with survey development, study design, and manuscript revisions.
- KY assisted with survey development, study design, and manuscript revisions.

3. The paper reported in Chapter 4:

de Graaff, B., Neil, A. Sanderson K, Yee, K.C. & Palmer AJ. "Costs associated with hereditary haemochromatosis in Australia: A cost of illness study" *Australian Health Review*: Accepted for publication.

- BdG undertook study design, development of the survey, submission for ethical approval, recruitment, data management and analysis. BdG drafted the manuscript and coordinated revisions and submission.
- AP assisted with conceptualisation of the study, assisted with study design, survey development, interpretation of data analyses and manuscript revisions.
- AN assisted with survey development, study design, survey development, interpretation of data analyses and manuscript revisions.
- KS assisted with survey development, study design, and manuscript revisions.
- KY assisted with survey development, study design, and manuscript revisions.

4. The paper reported in Chapter 5:

de Graaff, B., Lei, S., Neil, A., Yee, K.C., Sanderson, K., Gurrin, L.C. & Palmer AJ. **"**Population screening for hereditary haemochromatosis in Australia: construction and validation of a state-transition cost-effectiveness model" This manuscript has been submitted to *Applied Health Economics and Health Policy.*

- BdG conceptualised and constructed the health economics model and wrote the manuscript. BdG tested the model face validity, internal validity and external validity, conducted base-case analyses and model projections, coordinated revisions and submission.
- AP conceptualised the model, assisted with model construction, validation and analyses. AP assisted with interpretation of results and manuscript revisions.

- LS assisted in the construction and validation of the model, along with revisions of the manuscript.
- AN assisted with validating the model, interpretation of results and manuscript revisions.
- KY assisted with face validation of the model and manuscript revisions.
- KS reviewed the manuscript and assisted with revisions.
- LG assisted in acquisition of model parameter values, face validity and manuscript revision.

The paper reported in Chapter 6:

de Graaff, B., Neil, A., Lei, S., Yee, K.C., Sanderson, K., Gurrin, L.C. & Palmer AJ. "Cost-effectiveness of different population screening strategies for hereditary haemochromatosis in Australia" This manuscript has been submitted to *Applied Health Economics and Health Policy.*

- BdG conceptualised and constructed the health economics model, conducted the base-case analyses, one-way and probabilistic sensitivity analyses. BdG wrote the manuscript and coordinated revisions and submissions.
- AP assisted in the conceptualisation and construction of the model, provided advice on conducting analyses and interpreting the results. AP assisted with manuscript revisions.
- AN assisted with interpretation of results and manuscript revisions.
- Lei Si assisted in the construction of the model and with revisions of the manuscript.
- KY reviewed the manuscript and assisted with revisions.
- KS reviewed the manuscript and assisted with revisions.
- LG assisted in acquisition of model parameter values and manuscript revision.

Statement of co-authorship

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Statement of ethical conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

Signature

7-7-16

Date

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I have been enormously fortunate to have been provided with the opportunity to undertake my PhD at Menzies Institute for Medical Research, in a field which I find highly exciting. I have been fortunate to work on a project that has allowed me to collaborate with researchers, clinicians and a patient group. I would like to take this opportunity to thank Menzies and the University of Tasmania for this opportunity.

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Abstract

Haemochromatosis is one of the most common autosomal recessive disorders amongst populations of northern European ancestry. It is a condition characterised by iron overload, which, if untreated, contributes to morbidity and mortality. As diagnosis is often delayed owing to the non-specific nature of early symptoms, population screening programs have been suggested to reduce the consequential burden of disease. To date, a paucity of robust health economic evidence regarding haemochromatosis screening has been cited as a key barrier to the establishment of such programs internationally. This thesis investigates and generates health economic evidence for haemochromatosis and related interventions, with a focus on population screening programs.

Chapter 1 presents a general overview of haemochromatosis and health economic concepts pertinent to this thesis.

Chapter 2 presents a systematic review of all health economic evidence regarding haemochromatosis screening and related interventions. Most of the evidence identified in the review related to population screening programs. The economic methodologies employed and the quality of epidemiologic evidence incorporated into these models were flawed in most studies, reducing their validity and generalizability. The gaps in current knowledge that were identified in this review guided the subsequent direction of this thesis.

The systematic review did not identify any robust health state utility value data for haemochromatosis. Whilst four studies included in the review incorporated utility values into cost-effectiveness models, these were set at unrealistically high levels, with no description of the source of these provided. Chapter 3 aimed to robustly quantify the quality of life burden associated with haemochromatosis by measuring health state utility values. A national, online survey of people with haemochromatosis was conducted, which allowed for calculation of utilities for different categories of severity of haemochromatosis. These utility values, which provide insight into the quality of life impacts of haemochromatosis, were incorporated into the population screening model.

In the absence of published literature quantifying the economic burden associated with haemochromatosis, a national cost of illness study was undertaken, and is reported in Chapter 4. Costs were estimated from the patient, government and societal perspectives, with societal costs extrapolated to the Australian population. These costs are the first to be published that quantify the economic burden of haemochromatosis. Whilst Chapters 3 and 4 provide information on the size of the burden associated with haemochromatosis, Chapter 6 identifies

strategies to address this.

Chapter 5 provides a detailed description of the construction and validation of the health economic model for screening for haemochromatosis. A state-transition Markov model using probabilistic decision analysis was constructed and validated for the Australian adult population of northern European ancestry.

Chapter 6 presents the results generated from the health economics model. The target populations were males aged 30 years and females aged 45 years, both of northern European ancestry, and neonates irrespective of ancestry. Three population screening strategies (genotyping with a blood sample, genotyping with a buccal sample, sequential screening with two consecutive iron studies and confirmatory *HFE* genotyping) were modelled for adults and one for neonates (*HFE* genotyping). The current *status quo* was the comparator, which comprises a combination of cascade and opportunistic screening. From the government perspective, genotyping with a blood sample was the most cost-effective approach for males; for females, sequential screening was considered to be the most cost-effective. For male and female neonates, screening was associated with cost savings and increased effectiveness, thereby dominating the current *status quo*.

This thesis presents a range of studies that were conducted to address the substantial knowledge gaps identified in the systematic review. Both the health state utility data and cost of illness data can be used to populate future health economic models regarding haemochromatosis interventions. The results of the modelling work provide medical and reimbursement decision-makers with robust data when considering future resource allocation decisions pertaining to screening for haemochromatosis.

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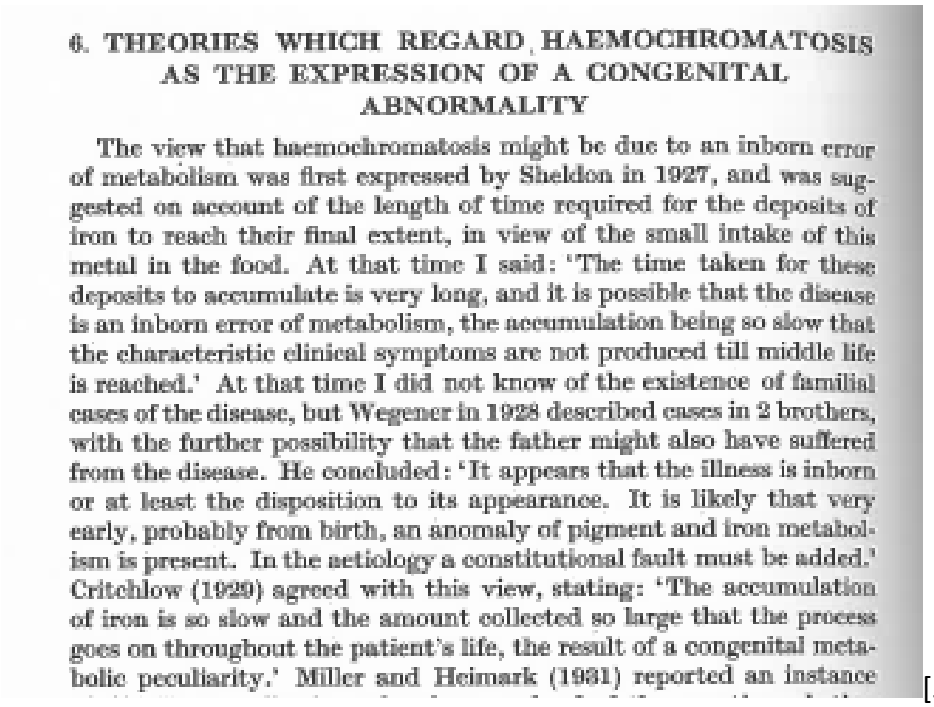
Chapter 1: Introduction and outline

1.1 Introduction to hereditary haemochromatosis

High Iron Fe (*HFE*)-associated hereditary haemochromatosis is one of the most common autosomal recessive disorders amongst populations of northern European ancestry. Clinically it is characterised by excessive absorption of dietary iron, which is predominantly stored in the parenchymal tissue of the heart, liver and pancreas, leading to increased morbidity and mortality [1-3].

Iron overload related to haemochromatosis was first identified in 1889 by a German pathologist, Dr Frederich von Recklinghausen [4]. In a book published in 1935, the English gerontologist Dr Joseph Sheldon reported haemochromatosis to be a rare condition with an estimated prevalence of between 1 in 2,000 and 1 in 5,000. He claims to be the first to link haemochromatosis with an inborn metabolic disorder, as described in an excerpt of his book below.

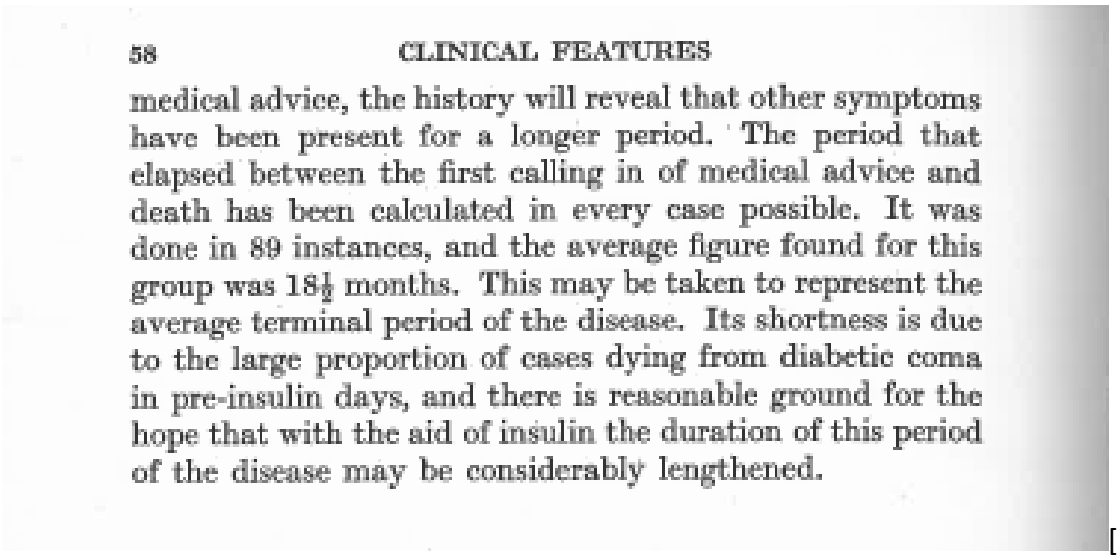


6. THEORIES WHICH REGARD HAEMOCHROMATOSIS AS THE EXPRESSION OF A CONGENITAL ABNORMALITY

The view that haemochromatosis might be due to an inborn error of metabolism was first expressed by Sheldon in 1927, and was suggested on account of the length of time required for the deposits of iron to reach their final extent, in view of the small intake of this metal in the food. At that time I said: 'The time taken for these deposits to accumulate is very long, and it is possible that the disease is an inborn error of metabolism, the accumulation being so slow that the characteristic clinical symptoms are not produced till middle life is reached.' At that time I did not know of the existence of familial cases of the disease, but Wegener in 1928 described cases in 2 brothers, with the further possibility that the father might also have suffered from the disease. He concluded: 'It appears that the illness is inborn or at least the disposition to its appearance. It is likely that very early, probably from birth, an anomaly of pigment and iron metabolism is present. In the aetiology a constitutional fault must be added.' Critchlow (1929) agreed with this view, stating: 'The accumulation of iron is so slow and the amount collected so large that the process goes on throughout the patient's life, the result of a congenital metabolic peculiarity.' Miller and Heimark (1931) reported an instance

[5]

Sheldon conducted a review of case studies of haemochromatosis patients and noted that proceeding diagnosis, most patients experienced complications related to infections and diabetes. Due to an absence of effective treatments, predominantly for diabetes, most patients died within 18 months of diagnosis [5].



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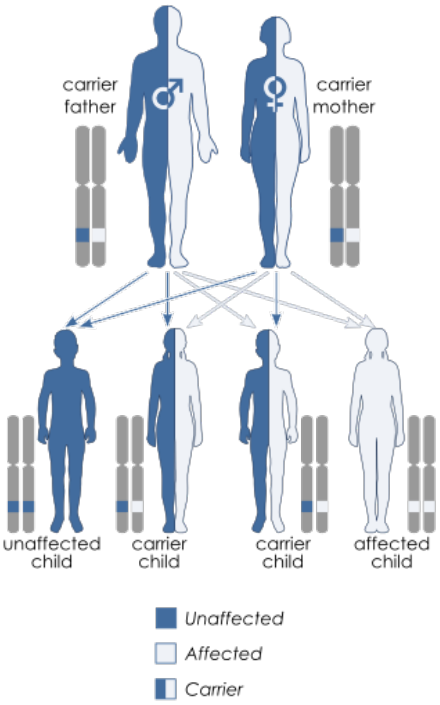
medical advice, the history will reveal that other symptoms have been present for a longer period. The period that elapsed between the first calling in of medical advice and death has been calculated in every case possible. It was done in 89 instances, and the average figure found for this group was 18½ months. This may be taken to represent the average terminal period of the disease. Its shortness is due to the large proportion of cases dying from diabetic coma in pre-insulin days, and there is reasonable ground for the hope that with the aid of insulin the duration of this period of the disease may be considerably lengthened.

[5]

In 1952, two English physicians by the names of Davis and Arrowsmith documented the effectiveness of venesection as a treatment for iron overload related to haemochromatosis [6]. More than two decades later, haemochromatosis was shown to involve the human leukocyte antigen (HLA), which provided clear evidence that the condition was inheritable [7]. This discovery was followed by that of Feder and colleagues who, in 1996, identified a mutation of the *HFE* gene that was associated with haemochromatosis [8]. Whilst several mutations of this gene that are associated with haemochromatosis have since been identified (e.g. C282Y, H63D, S56C), C282Y homozygotes account for between 80 and 90% of the burden of disease [9, 10].

Hereditary haemochromatosis is an autosomal recessive genetic disorder. For disease to occur (i.e. iron overload and related co-morbidities), two copies of the mutated gene must be present. For two unaffected parents who are both carriers of a *HFE* mutation, there is a 25% chance that each child will be homozygous for a haemochromatosis mutation, or a compound heterozygote involving two of these mutations (Figure 1.1).

Figure 1.1: Autosomal recessive inheritance (reproduced from Kashmiri [11])



1.1.1 Prevalence of haemochromatosis

Prevalence of the most commonly documented mutations of the *HFE* gene – C282Y and H63D – vary by racial ancestry, as displayed in Table 1.1. Amongst populations of northern European ancestry, the prevalence of C282Y homozygosity is estimated to range between 0.68% and 0.74% [12, 13]. A lower estimate has been reported for Caucasians (0.44%) as this population group is not limited to northern Europeans [10]. The prevalence rate of the C282Y genotype is notably lower for Native Americans (0.11%), Hispanics (0.027%), African Americans (0.014%) and Pacific Islanders (0.012%) [10]. In contrast, amongst Asian populations, the estimated prevalence is just 0.000039%, and no C282Y homozygote mutations were reported for two small populations of Aboriginal Australians [10, 14]. As haemochromatosis is an autosomal recessive disorder, a carrier of the C282Y gene in combination with a wild-type gene (i.e. no mutation) will not experience iron-overload related to haemochromatosis. The estimated carrier prevalence rate for populations of northern European ancestry is 10% [10].

The prevalence rates for H63D homozygotes and compound heterozygotes (C282Y/H63D) are greater than for C282Y homozygotes (Table 1.1). For example, amongst Caucasians prevalence of H63D homozygosity has been estimated to be 2.4% [10], and in comparison with C282Y homozygosity prevalence, is higher for all other ancestry groups. However, dramatically lower clinical penetrance is associated with these genotypes, accounting for approximately 10% of the burden of disease [9, 15].

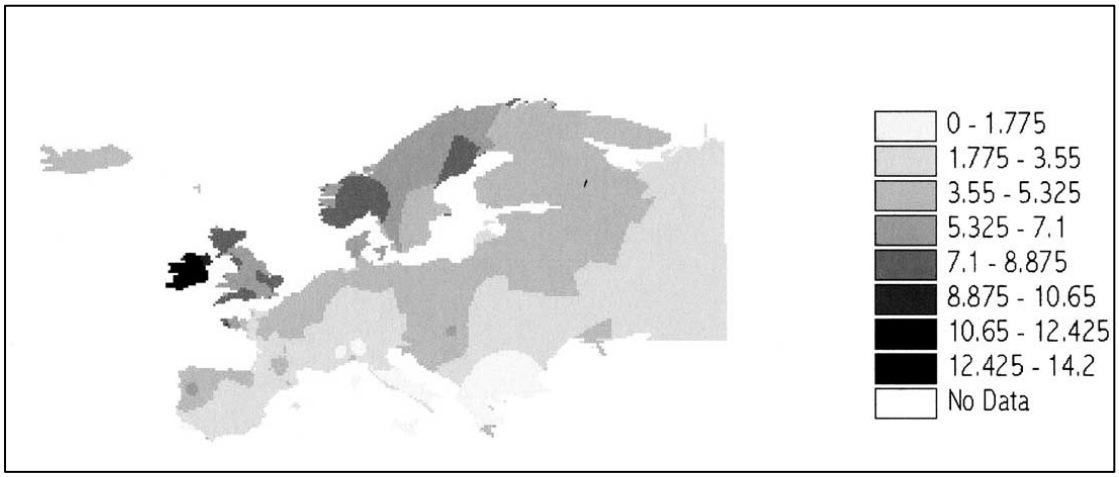
Table 1.1: Prevalence of common HFE mutations by ancestry groups

Study population	C282Y/C282Y (%)	H63D/H63D (%)	C282Y/H63D (%)
Northern European	0.68 [12]	1.89[16]	2.4 [12]
Caucasians	0.44 [10]	2.4 [10]	2.0 [10]
Native Americans	0.11 [10]	1.3 [10]	0.77 [10]
Hispanics	0.027 [10]	1.1 [10]	0.33 [10]
African Americans	0.014 [10]	0.089 [10]	0.071 [10]
Pacific Islanders	0.012 [10]	0.20 [10]	0.096 [10]
Asian	0.000039 [10]	0.20 [10]	0.0055 [10]
Aboriginal Australian	0 [14]	0.52 [14]	n/r

n/r: not reported

To put this ancestry-dependent prevalence into context, it has been hypothesised that the C282Y mutation first occurred in northern Europe, most likely either in the British Isles or Scandinavia [17]. The allele frequency map in Figure 1.2 [17] clearly shows the highest frequencies of the C282Y allele have been identified in Ireland and Finistère, a department in the westernmost part of France, followed by regions of the United Kingdom and Scandinavia. A study of the mitochondrial DNA of C282Y homozygotes found that the C282Y mutation likely occurred subsequent to human migration from Africa into Europe, approximately 4,000 years ago [18]. Further, the C282Y mutation can be dated back approximately 70 generations [19], and may have been an adaptive mutation in an environment in which dietary iron was scarce.

Figure 1.2: European distribution of the C282Y mutation (reproduced from Lucotte & Dieterlen, pp 263 [17])



1.1.2 Penetrance of haemochromatosis

Estimates of the clinical penetrance rate (i.e. those with the mutation exhibiting symptoms) of haemochromatosis have varied greatly since the 1935 publication of Joseph Sheldon's work. At that time, it was considered a largely fatal disorder, with most patients dying within two years of diagnosis, due to irreversible organ damage and lack of treatments [5]. As a result of ongoing research and development of clinical interventions, haemochromatosis today is infrequently a fatal condition. Increased awareness of the condition combined with effective diagnostic tests and treatment leading to improved patient outcomes.

Over the past two decades reported rates of clinical penetrance for C282Y homozygotes have varied between 2% and 76% [9, 12, 20-33]. This variation is in part due to different definitions of penetrance being employed. Penetrance has been variably defined as: cirrhosis of the liver and hepatocellular carcinoma; multiple signs, symptoms and comorbidities including elevated iron studies, fatigue, and arthritis; through to irreversible organ damage. This variation has resulted in a somewhat unclear body of literature pertaining to penetrance. To address this uncertainty, the European Association for the Study of the Liver published a Consensus paper in 2000 recommending the use of four stages or categories of haemochromatosis [34]. These categories, outlined in Table 1.2, allow for capture of all aspects of haemochromatosis, and

adoption of these will improve the generalizability and communication of research in this field. These categorise have been adopted throughout this thesis, in order to clearly define penetrance of *HFE*-haemochromatosis.

Table 1.2: Categories of haemochromatosis[34]

Category 1	Genetic mutation only (C282Y homozygotes, H63D heterozygotes and compound heterozygotes)
Category 2	Genetic mutation and elevated iron studies, either transferrin saturation or serum iron
Category 3	Genetic mutation, elevated iron levels and early symptoms (e.g. arthritis, fatigue, lethargy)
Category 4	Genetic mutation, elevated iron levels and organ damage (e.g. liver cirrhosis, hepatocellular carcinoma, heart disease, Type 2 diabetes)

To date, only a small number of studies have published data based on these categories. A large Australian study of people with haemochromatosis used Categories 3 and 4 to define clinical penetrance [12]. Amongst this random sample, a penetrance rate of 13.9% was reported for C282Y homozygotes, with sex-specific rates of 28.4% for males and 1.2% for females. The lower penetrance observed for females is largely due to menstruation, which reduces iron stores on a regular basis [32, 35, 36]. A second study using these four categories was based on a French haemochromatosis registry [37]. Categories 2, 3 and 4 were all defined as clinical penetrance: 24% of registry patients were assessed as being in Category 2, 58% in Category 3 and 18% in Category 4. This was not, however, a representative sample, as it was likely that patients on the register had been diagnosed with haemochromatosis due to being symptomatic, therefore resulting in an under-estimate of the proportion of patients in Category 1.

Recent work has focused on identifying variants of genes other than *HFE* that, when present with a homozygous C282Y mutation, mediates the likelihood of iron-overload, i.e. penetrance. To date, promising work has focused on a variant of the GNPAT gene [38-40]. DNA sequencing of C282Y homozygotes with either severe iron overload or no iron overload

showed that presence of this variation (GNPAT p.D519G) was associated with the iron-overloaded group [40].

1.1.3 Diagnosis of haemochromatosis

Diagnosis of haemochromatosis is typically carried out using a combination of serum iron studies and *HFE* genotyping, with approaches similar across countries. The Australian guidelines for diagnosis of haemochromatosis specify two patient groups: first degree relatives of a person diagnosed with haemochromatosis and those identified incidentally [41, 42]. For a first degree relative, diagnosis initially occurs through *HFE* genotyping, which, if found to be positive for a haemochromatosis-related mutation, is followed by iron studies. For the other patient group, diagnosis occurs sequentially: two elevated transferrin saturation tests and/or serum ferritin (the second fasting), followed by confirmatory *HFE* genotyping. Prior to the availability of genotyping, liver biopsies were commonly used to confirm a diagnosis of haemochromatosis. Similarly, the guidelines published by American Association for the Study of Liver Diseases recommends diagnosis by conducting iron studies, specifically transferrin saturation and serum ferritin, followed by *HFE* genotyping if elevated. Alternately, for first degree relatives of a haemochromatosis patient, simultaneous genotyping and iron studies should be conducted [43]. In the UK, recommendations for screening are similar, in that diagnosis is recommended by sequential iron studies (the second fasting), with a focus on transferrin saturation. If both results are elevated, confirmatory *HFE* genotyping is recommended [44].

1.1.4 Treatment of haemochromatosis

Treatment for haemochromatosis related iron overload focuses on reducing iron stores. When a patient commences treatment prior to organ damage, normal life expectancy is retained [45]. The most common treatment for iron overload is therapeutic venesection. Venesection typically involves removal of 500ml of blood, which equates to removal of 200 to 250mg of iron from bodily stores [43, 46, 47]. Depending on the extent of iron overload at diagnosis, venesection can be required on a weekly to fortnightly basis for up to two years to return iron stores to a therapeutic range. This initial stage of treatment is completed when serum ferritin is in the low normal range: 20-50µg/L; or a sustained decrease in haemoglobin

to under 11g/dl has been reached [42, 46]. At this point, maintenance treatment commences, involving venesection three to four times annually with regular monitoring of iron status. Whilst no randomised controlled trials have been conducted for this treatment, its effectiveness from observational research has been well-documented [33, 44, 48, 49], and ethical considerations preclude controlled trials.

A small proportion of patients do not tolerate venesection, experiencing negative effects such as fatigue and vasovagal reactions [50], and it is contraindicated in patients with severe cardiac disease and hypoproteinaemia [51, 52]. For these patients, iron chelation therapy and erythrocytapheresis are alternatives. There are three forms of iron chelation therapy: deferoxamine which is provided parenterally, and two oral agents: deferiprone and deferasirox. Deferasirox is the most recent iron chelation therapy to be made available, and marks a substantial improvement from the earlier formulations, as it requires once daily dosing with an oral tablet in a community-based setting. In contrast, deferoxamine is administered parenterally as an infusion, in some cases for 12 hours per day, five days per week. Deferiprone is available in liquid and tablet form, and frequently taken three times daily [46]. Whilst all three iron chelation agents result in reduced iron stores, adverse events such as increased local skin reactions, susceptibility to infections, cataracts, ototoxicity and transient renal failure have been reported [46, 53].

Erythrocytapheresis is an alternative treatment for iron overload which involves apheresis in which the erythrocytes are removed from the whole blood; an effective approach to reducing iron stores. In a randomised controlled trial (RCT), this form of treatment was compared to venesection in a cohort of recently diagnosed haemochromatosis patients. The authors reported a significantly reduced number of treatments for the erythrocytapheresis group to return to therapeutic iron levels, however the economic costs associated with this treatment were 3.5 times that of venesection [50].

The point at which treatment should commence, i.e. when the patient is iron-overloaded, is unclear in the literature. In 2000 the European Association for the Study of the Liver (EASL)

published a consensus statement on haemochromatosis noting that guidelines on commencement of treatment were based on empirical evidence in most countries [34]. As a result, there are limited cut-off points for results of serum ferritin or transferrin saturation tests that indicate treatment. Serum ferritin of 300µg/l for males and menopausal women and 200µg/l for pre-menopausal women are considered markers of iron-overload [54], however, inflammation, cytolysis and excessive intake of alcohol can also increase serum ferritin [46]. It is accepted that when serum ferritin is ≥1,000µg/l, treatment is clearly indicated. However, for haemochromatosis patients with serum ferritin in the ranges of 200-1,000µg/l in pre-menopausal females and 300-1,000µg/l in other patients, the point at which to commence treatment is less clear. Patient preference and clinical judgement are recommended to guide such decision-making [47].

Transferrin saturation is considered the most useful test for diagnosing iron overload [21, 44, 46]. In many settings, two consecutive elevated transferrin saturation tests are conducted, the second fasting [42]. The cut-off ranges that have been suggested as indicative of iron-overload, and therefore treatment, are 55% for males and between 45% [43] and 50% for females and 55% for males [44, 46, 55].

1.2 Introduction to health economics

Health economics is the study of scarcity and resource allocation in the health sector. It is a specialist field of economics, which incorporates many elements of microeconomic theory [56]. The seminal paper published in 1963 by Kenneth Arrow has been credited as marking the birth of health economics [57]. Arrow argued that the 'medical care industry' was characterized by unique factors such as significant government intervention and asymmetric information, unlike other fields of study in economics. From this point on, health economics developed into a specialist field within the discipline of economics.

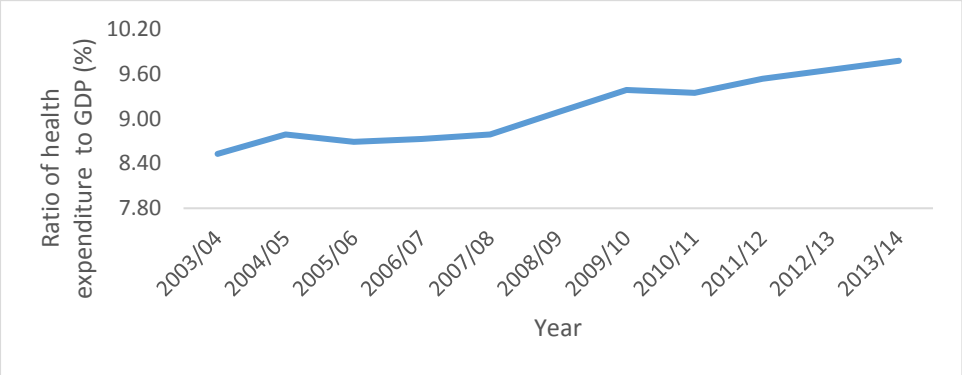
1.2.1 Economics and/of the healthcare sector

The proportion of gross domestic product (GDP) spent on health in developed countries has grown in recent decades. The average proportion of health spending (as a proportion of GDP)

in countries that are members of the Organisation for Economic Co-operation and Development (OECD) increased from 7.3% in 2000 to 8.9% in 2013 [58, 59]. Whilst the Global Financial Crisis has slowed growth rates in many European countries, the demand for health services has not followed this trend [60].

In Australia, the ratio of health expenditure to GDP has increased from 8.53% in 2003/04 to 9.78% in 2013/14 (Figure 1.3) [61]. There are several factors that underpin this growth. Demographic change, in the form of an ageing population, is considered a major driver of increased expenditure in many developed countries [59], as health expenditure is substantially higher for older adults than children. In 2008/09, Australian expenditure per person was approximately 20 times higher for adults aged 85 years or older than for children aged between ages 5 and 14 years [62]. Other important drivers of growth in health expenditure include technological advancements and increased consumer expectations [63, 64].

Figure 1.3: Ratio of health expenditure to GDP, Australia 2003/04-2013/14 [61]



1.2.2 Key concepts in health economics

Whilst a full exploration of health economic concepts is beyond the scope of this chapter, a brief discussion of key concepts provides background to the conceptual and methodological approaches employed in this thesis.

Opportunity cost

Limited resources result in the need to make choices between viable alternatives, which are

often mutually exclusive [63]. The opportunity cost of the choice is the value of the next best alternative forgone [65]. The opportunity costs associated with health funding decisions are often measured using health economic evaluations such as cost effectiveness analyses [66].

Efficiency

There are three primary types of efficiency that are considered in health economic evaluations: Pareto or allocative, technical and cost efficiency [67]. Efficiency is related to opportunity cost and can be defined as either maximizing the output for an opportunity cost, or alternately, minimizing the opportunity cost of producing an output [63]. When a state of resource allocation is achieved at which point it is impossible to reallocate resources without causing an uncompensated reduction in the wellbeing or utility of another individual, this is referred to as Pareto-efficiency or alternatively, allocative efficiency [63]. Technical efficiency refers to the relationship between resources and, in the health sector, health outcomes. Technical efficiency is achieved when the maximum achievable output is produced using the resources that are technically necessary to produce that output [63, 68]. Lastly, cost efficiency refers to a state in which an output is produced using the least costly combination of resources whilst maintaining technical efficiency [63, 69].

Health Equity

Health equity refers to the absence of avoidable disparities in health, irrespective of the social, demographic, economic or geographic characteristics [70], and is an important consideration in health policy and resource allocation decisions. Equity is informed by a range of theoretical approaches such as egalitarianism and libertarianism. The prevailing approach espoused by a society will govern the manner in which equity is considered. In Australian society, egalitarianism has been the dominant philosophical approach underpinning cultural and political attitudes and policy [71]. The most notable outcome of this in the health sector is the national public health insurance scheme (Medicare) that is available to all Australian citizens, irrespective of income or wealth. Health equity in a country such as Australia is based on the notion that all people should have the opportunity to attain their full health potential in the absence of systematic disparities [72].

Value in health care

The growth in health expenditure has contributed to an increased focus on ensuring value in health care expenditure [73]. Value, in this context, refers to the desirability of an intervention, technology or resource due to the benefits associated with it, such as enhanced effectiveness. Building on this, value in health care (expenditure) is measured by outcomes and costs, rather than metrics such as number of surgeries performed or the number of nurses employed [74]. Value in health care (expenditure) refers to all stakeholders working together to maximize the efficient use of resources to achieve outcomes needed by patients or the community [63]. The field of health economics is well-placed to contribute to this change in focus. Data from high quality clinical and epidemiological studies can be incorporated into economic analyses to help inform decisions around health resourcing to maximize value in decision making.

1.2.3 Health economic evaluations

One of the primary purposes of conducting economic evaluations in the health care sector is to inform the decision making process regarding the efficient use of limited resources [69]. To this end, health economic evaluations must involve the quantification of the costs and effectiveness associated with an intervention or policy and the next best alternative, so called full economic evaluations.

There are three commonly used forms of full economic evaluations: cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis. Cost-benefit analyses measure the resources used to provide an intervention and the outcomes associated with it, in monetary units. The underlying principle of this form of analysis is that if the benefits are greater than the costs, social welfare will be improved [64]. One of the limitations inherent in this approach is the need to value benefits or outcomes in monetary units, which can be difficult to accomplish in some circumstances [69]. In several cost-benefit analyses, a value of 100,000 United State Dollars (USD) has been used for one year of life, and USD6 million for a human life [75]. Calculating the value of a human life is a difficult task from both technical and philosophical perspectives [64, 76].

Cost-effectiveness analysis avoids the need to value outcomes or effects in monetary units, instead measuring these in health units. There are two forms of cost-effectiveness analysis: the standard approach measuring effectiveness on a unidimensional scale (such as life years gained or cases detected), and cost-utility analysis, which employs measures of effectiveness such as quality adjusted life years (QALYs). QALYs combine quality of life with quantity of life, and allow for comparison across different interventions (see Section 1.2.5).

There are also several forms of partial economic evaluations, but these cannot be used to inform questions of efficiency. Partial health economic evaluations are limited to consideration of the costs associated with one of more intervention or health state, or alternatively, they evaluate the costs and consequences of one intervention with no comparator [77]. A cost of illness study, a commonly conducted form of economic analysis, quantifies the economic burden associated with a condition.

In all forms of economic analysis, a perspective is adopted, such as that of the payer, the patient or society. Relevant costs associated with the condition of study are then calculated and reported from that perspective. Different types of costs can be reported, depending on the aim of the study. Over the past 20 years, development regarding the concepts and terminology around types of costs has occurred. As health economics has its foundations in the field of economics, costs have commonly been reported using conventional terminology of direct, indirect and intangible costs. It is generally agreed that direct costs include all costs arising from the utilization of goods and services related to a health condition or an intervention of study. Over recent years, there has been an increasing number of papers published that have broken these costs down to health sector and other sector costs to further increase understanding of where costs are incurred [78-80]. Indirect costs typically refer to productivity losses or time-loss costs, which are calculated using either the human capital approach or the friction cost method [81]. The human capital approach includes all time not worked as lost productivity, whereas the friction cost method only counts productivity loss for the time until another worker can take over the role. There are several aspects of costing that continue to be debated, with no clear consensus achieved. The approach to cost studies adopted in this study is that it is best informed by the target audience

of the analysis, the population and the intervention or disease being studied.

1.2.4 Health state utility values

Utility, in health economics, refers to an individual or society's preference for specific health-related states and are used as the quality of life component in calculating a QALY [63, 69]. Utility may be measured in multiple ways, some of the more common approaches are time-trade off and standard gamble exercises, and multi-attribute utility instruments (MAUIs) [82].

The time trade-off approach involves providing participants with two alternatives: a chronic health state for time *t* (life expectancy for the chronic condition), and full health for *x* amount of time, followed by death. The amount of time (*x*) in full health is varied until the participant becomes indifferent to the alternatives. The utility is thus derived: *x/t.*

An alternative approach is the standard gamble in which participants are provided with two alternatives to choose between. The first alternative has two probability-based outcomes: returning to full health after *t* years (probability=*p*), or immediate death (probability=1-*p*). The second alternative is a certain outcome in which the participant remains in a chronic health state for life. The probability (*p*) is varied until the participant is indifferent towards the alternatives. The utility score for the condition of interest is this final probability [63, 69].

MAUIs are commonly used in cost-effectiveness analyses as they provide a straightforward approach to measuring utilities [83]. The most commonly used MAUIs are the EuroQol-5D (EQ-5D), Short-Form 6D (SF-6D) and Health Utilities Index (HUI) instruments. The Assessment of Quality of Life (AQoL) instruments, which were developed in Australia, have been gaining popularity in recent years due to their superior level of sensitivity to various health states, particularly those with a psychosocial component [84]. Whilst each MAUI has their strengths and limitations, they provide an effective method to elicit utility data from clinical and epidemiological studies.

1.2.5 Quality adjusted life years (QALYs)

QALYs are a commonly used measure of effectiveness in cost-utility analyses. National funding bodies such as the the Australian Government's Medical Services Advisory Council

(MSAC) and the Pharmaceutical Benefits Advisory Council (PBAC) and the UK's National Institute for Health and Care Excellence (NICE) prefer QALYs to be included in assessments of new technologies and interventions. The QALY provides a metric that allows for comparison across different interventions. Calculation of a QALY is carried out with the following formula:

$$QALY = 1 \times U$$

Where *U* is the utility value associated with that year of life. A QALY can be calculated over multiple years using the formula:

$$\text{QALY} = \sum_{t=1}^{T=max} \frac{F^i U^i}{(1+d)^t}$$

Where F^i is the function of the probability that the individual is alive at each year, *d* is the discount rate (see Section 1.2.8) and U^i is the utility value for each year [85]. This measure facilitates the quantification of the differences in effectiveness between two interventions with differing morbidity and/or mortality impacts, allowing for the calculation of an incremental cost-effectiveness ratio (ICER).

1.2.6 Incremental cost-effectiveness ratio (ICER)

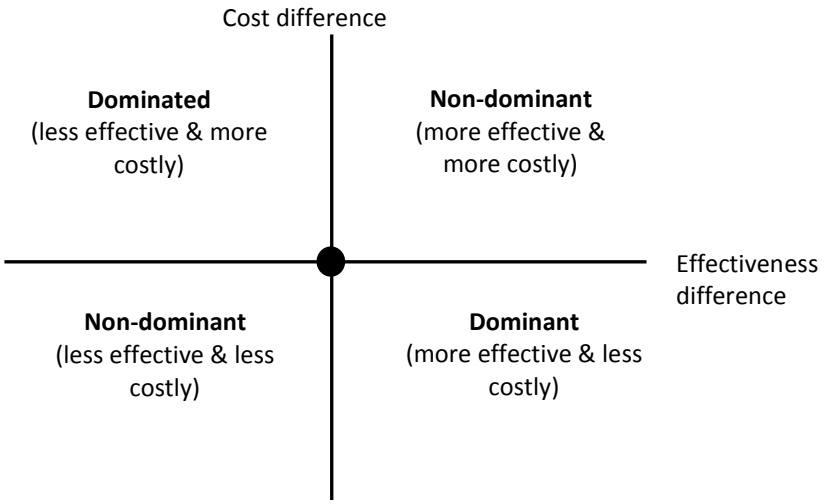
An ICER is a summary statistic of the cost-effectiveness of an intervention, and estimates the cost associated with the gain of one additional QALY. The numerator of the ICER incorporates the costs of the *status quo* or other comparator subtracted from the cost associated with the new intervention. Cost-offsets related to a new treatment should be taken into account. The denominator comprises the effectiveness associated with the *status quo* subtracted from the effectiveness associated with the new intervention. This allows for the calculation of an ICER associated with the new intervention. The formula to calculate an ICER is:

$$ICER = \frac{\text{Cost}\ (new) - \text{Cost}\ (status\ quo)}{\text{Effectiveness}\ (new) - \text{Effectiveness}\ (status\ quo)}$$

A cost-effectiveness plane is a useful way of understanding potential ICERs (Figure 1.4). If the new intervention is less costly and more effective than the *status quo* (which sits at the point

where the *x* and *y* axes intercept), then the new intervention is said to dominate the *status quo.* Alternately, if the new intervention is more costly and less effective, then it is dominated by the *status quo*. Frequently, a new intervention will be in the remaining two quadrants: either more costly and more effective, or less effective and less costly, than the *status quo*.

Figure 1.4: Cost-effectiveness plane [86]



1.2.7 Willingness to pay

A common measure in health economics, willingness-to-pay (WTP) refers to the maximum value an individual and in turn society is willing to pay for a good or service [87]. In health economics, a WTP threshold is commonly used to represent what a society (often through a government) is willing to pay for an intervention that delivers an incremental gain of one QALY in comparison to the *status quo* [88]. This threshold represents a theoretical point at which an intervention is considered cost-effective. In Australia, no WTP threshold has been officially specified, however an unofficial threshold of AUD50,000 per QALY gained is often cited [89, 90]. In the United States, thresholds of between USD50,000 to 100,000 are used, and £20,000-30,000 in the United Kingdom [88].

1.2.8 Discounting

Discounting is carried out in health economic evaluations to report future costs and effects as their present value. Discounting reflects a greater value placed on present costs and health effects than those accrued in the future – time preference [69]. For health technology

assessments, the recommended discount rate for costs and effects varies by countries. In the US a discount rate of 3% is recommended [91], a rate of 3.5% is recommended in the UK [92], and in Australia, a higher rate of 5% is recommended [93]. The formula to discount a cost or effect in arrears is:

$$Present\ value = \frac{X}{(1+r)t}$$

where *X* is the outcome of interest (the cost of effect), *r* is the discount rate and *t* is the time, commonly the number of years in the future.

1.2.9 Economic modelling in health economic evaluations

Modelling is an approach applied in health economic evaluations that allows for the extrapolation of costs and health outcomes in the absence of real-world data. This is a particularly useful approach when it is improbable that real-world data can be obtained due to resourcing, ethical or time horizon considerations [94]. Modelling allows for the comparison of multiple interventions over variable time horizons within hypothetical cohorts.

Decision tree analysis is a commonly used approach in health economic modelling. The structure of a decision tree represents potential clinical pathways, with preferably evidence-based estimates of the likelihood of particular events occurring governing progress of the hypothetical cohort through the tree. The probabilities of events will be influenced by the interventions being considered. In turn the costs and effectiveness of competing interventions, and their ICERs can be calculated.

An advanced form of a decision tree is the Markov model. This type of model consists of discrete states which the hypothetical cohort can move between over time. Movement between these Markov states is guided by transition probabilities. Each movement by the cohort occurs over a discrete time period (e.g. 1 year), referred to as a 'Markov cycle'. Upon completion of one Markov cycle, the cohort commences a subsequent cycle in the Markov states determined by the transition probabilities for the Markov state they were just in. Movements or transitions will occur for a predetermined number of cycles or until everyone transitions into an absorbing state. The key feature of the Markov model is 'memorylessness',

in that transition between states is independent of past or future states, allowing for stochastic progress through the model. This is particularly useful when modelling chronic health states such as haemochromatosis.

1.2.10 Summary of health economics

Health economic evaluations provide important information that can aid decision makers in the decision making process This thesis brings together many of the concepts introduced above, in order to establish health economic evidence for screening for haemochromatosis. This evidence encompasses the quantification of both the economic and health-related quality of life burdens associated with the condition, and the cost-effectiveness of population-based screening for haemochromatosis in Australia.

1.3 What is the need for health economic evaluations of haemochromatosis and related interventions in Australia?

Population screening programs for hereditary haemochromatosis have been proposed in several countries with high rates of prevalence [28, 34, 95-98]. Decisions regarding the implementation of population screening programs are largely based on the screening criteria published by Wilson and Jungner in 1968 (Textbox 1) [99] . Haemochromatosis is a condition that meets these criteria [100], with the exception of criterion point 9: 'The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole' [99]. To date, a lack of robust health economic evidence for haemochromatosis screening programs has been cited as a barrier to implementation of such a program [34, 101-103]. To address this, a systematic review was undertaken to evaluate the quality of health economic evidence for haemochromatosis screening (Chapter 1). Whilst almost all studies concluded that screening was cost-effective, most contained flawed assumptions and/or methodological limitations, thereby reducing the validity of the results. Further, four studies employed utility values of unidentified sources when evaluating the cost-effectiveness of screening. The values for health states including asymptomatic haemochromatosis, cirrhosis of the liver, heart disease and type 2 diabetes were higher than reported for comparable normative population utility

data, likely leading to underestimates in gains of effectiveness of screening. In addition, the systematic review did not identify any literature reporting on the economic burden associated with haemochromatosis. The conclusions of this review concurred with statements regarding the paucity of robust health economic evidence for screening for haemochromatosis. The gaps identified in this review informed the subsequent direction of the studies in this thesis, as outlined in Section 1.4.

Textbox 1: Wilson and Jungner's screening criteria [99]

1. The condition sought should be an important health problem;
2. There should be an accepted treatment for patients with recognized disease;
3. Facilities for diagnosis and treatment should be available;
4. There should be a recognizable latent or early symptomatic stage;
5. There should be a suitable test or examination;
6. The test should be acceptable to the population;
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood;
8. There should be an agreed policy on whom to treat as patients;
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole;
10. Case finding should be a continuing process and not a "once and for all" project.

1.4 Research objectives

The specific research aims examined within this thesis are outlined below:

1. To evaluate all published health economic evidence for hereditary haemochromatosis **(Chapter 2)**.
2. Quantify the health-related quality of life burden associated with hereditary haemochromatosis **(Chapter 3)**.
3. Quantify the economic burden associated with hereditary haemochromatosis in Australia, from the perspective of the patient, government and society **(Chapter 4)**.
4. Construct and validate a health economics model for haemochromatosis employing Australian specific cost and utility data **(Chapter 5)**.
5. Evaluate the cost-effectiveness of population screening programs for Australia **(Chapter 6)**.

1.5 Structure of this thesis

Chapter 1 provides an overview of hereditary haemochromatosis and health economic concepts.

Chapter 2 presents a systematic review of all health economic studies for hereditary haemochromatosis. Studies included are predominantly focused on economic aspects of screening interventions.

Chapter 3 presents data on the health-related quality of life burden associated with haemochromatosis using health state utility values.

Chapter 4 provides an estimate on the economic burden associated with haemochromatosis in Australia.

Chapter 5 describes the construction and validation of a new model for screening for haemochromatosis in Australia. This papers presents data on the projected life expectancy and lifetime costs of C282Y homozygotes, along with the costs associated with the current approach to screening in Australia.

Chapter 6 presents the results of the cost-effectiveness model for adult and neonatal screening strategies. Costs and effectiveness of each strategy are presented, along with an estimate of the number of correct diagnoses from each strategy.

Chapter 7 discusses and summarises the material presented in this thesis, and makes comments regarding the future directions for research in this field.

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Chapter 2: A systematic review and narrative synthesis of health economic studies conducted for hereditary haemochromatosis

2.1 Preface

This chapter describes a systematic review of all health economic data pertaining to haemochromatosis. The review summarises the interventions studied, methodological approaches employed, underpinning assumptions and a synthesis of results. Most of the identified literature related to the evaluation of the cost-effectiveness of population screening programs. The health economic methodologies employed and the quality of epidemiologic evidence incorporated into these models were flawed in many studies, reducing their validity and generalizability. The review highlighted gaps in the current literature, which informed the work presented in subsequent chapters.

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2.2 Abstract

Background: Hereditary haemochromatosis (HH) is a common genetic condition amongst people of northern European heritage. HH is associated with increased iron absorption leading to parenchymal organ damage and multiple arthropathies. Early diagnosis and treatment prevents complications. Population screening may increase early diagnosis, but no programs have been introduced internationally: a paucity of health economic data is often cited as a barrier.
***Objective*:** To conduct a systematic review of all health economic studies in HH.
Methods: Studies were identified through electronic searching of economic/biomedical databases. Any study on HH with original economic component was included. Study quality was formally assessed. Health economic data were extracted and analysed through narrative synthesis.
Results: Thirty-eight studies met the inclusion criteria. The majority of papers reported on costs or cost-effectiveness of screening programs. Whilst most concluded screening was cost-effective compared with no screening, methodological flaws limit the quality of these findings. Assumptions regarding clinical penetrance, effectiveness of screening, health state utility values (HSUVs), exclusion of early symptomatology (such as fatigue, lethargy and multiple arthropathies) and quantification of costs associated with HH were identified as key limitations. Treatment studies concluded therapeutic venepuncture was the most cost effective intervention.
***Conclusions*:** There is a paucity of high quality health economic studies relating to HH. The development of a comprehensive HH cost-effectiveness model utilising HSUVs is required to determine whether screening is worthwhile.

2.3 Introduction

Hereditary haemochromatosis (HH) is an autosomal recessive disorder characterised by increased iron absorption. It is one of the most common genetic disorders amongst people of northern European ancestry [1-3]. A defect in the HFE gene has been found to be the predominant cause of HH with several mutations identified: C282Y, H63D and S56C [4-6]. Between 80 and 90% of people diagnosed with iron-overload related to HH have been found to be homozygous for the C282Y mutation [7, 8]. The H63D and S56C mutations are less commonly associated with iron overload or related disease unless present with the C282Y mutation, i.e. a compound heterozygote [9, 10]. Prevalence of C282Y homozygosity is highest amongst people of northern European ancestry with a

prevalence of approximately 1 in 150 to 200, whilst in people of other ancestries it is considerably lower: 1 in 300 Hispanics; 1 in 1,000 Native Americans; 1 in 1,000, 000 Asians [10-14]. Amongst people of northern European ancestry, the prevalence of C282Y/H63D heterozygotes is relatively common, being found in approximately 1 in 50 people, i.e. 4 times as common than the C282Y homozygote, whilst C282Y/S56C heterozygote prevalence is approximately 1 in 200, i.e. as common as the C282Y homozygote [5, 15]. In turn, a much smaller proportion of these compound heterozygotes will develop iron overload as compared with the C282Y homozygotes.

Clinically, HH is characterised by increased serum iron and iron stores [2, 16, 17]. The excess iron is stored in the parenchymal tissues of the liver, heart and pancreas. Early symptoms of HH-related iron overload include fatigue, lethargy, loss of appetite, and joint pain, most commonly in the fingers [18, 19]. Subsequent symptoms may include multiple arthropathies, Type 2 diabetes, impotence, fibrosis, cirrhosis and carcinoma of the liver, and heart disease [20-24]. The rate of clinical penetrance of HH has been somewhat controversial in the literature. This is in large part due to different definitions of penetrance: some authors have defined HH penetrance as liver cirrhosis, whilst others have included elevated iron studies through to cirrhosis and hepatocellular carcinoma. Recent epidemiological literature has reported penetrance (defined as early symptoms through to irreversible organ damage) of C282Y homozygosity to be 28.4% for males and 1.2% for females [11].

HH is currently diagnosed through targeted and/or opportunistic iron studies, most commonly transferrin saturation (TfS) and serum ferritin (SF) (phenotyping). If TfS and SF are found to be elevated, in the absence of other contributing factors HH is suspected and a genetic test may be ordered (genotyping) [15, 25]. Treatment is effective and straightforward, consisting of regular therapeutic venepuncture (TV). If this is contraindicated, erythrocytapheresis is an alternative treatment in which red blood cells are separated from whole blood via apheresis [26].

Due to the non-specific nature of the early symptoms of iron overload (in that they can be experienced by people with iron levels within the clinically normal range), diagnosis is often delayed until after irreversible organ damage has occurred [27, 28]. Population screening programs have been suggested as a way to reduce the burden of disease associated with HH [29-38]. There are several options for HH screening, varying with regard to who should be screened: whole populations or sub-populations at greatest risk; and how they should be screened: genotyping and/or phenotyping.

The effectiveness of large scale screening for HH involves three main parameters: uptake of screening; sensitivity and specificity of screening tests; and adherence to treatment. Studies reporting on uptake of HH screening have been conducted in a wide range of settings with differing populations and screening techniques. Just one randomised controlled trial has been conducted, which involved random allocation of UK-based general practice patients to either phenotype or genotype screening [39]. In this study an uptake rate of 32% was reported. A pilot screening program in Australian schools reported an uptake rate of 33% [40], whilst a second Australian study investigating workplace screening reported 5.8% uptake [41]. In contrast to these studies, a large study in a Norwegian county which invited all inhabitants aged over 20 years of age to be screened for HH in combination with other conditions reported an uptake rate of 70% [42].

The sensitivity and specificity of biochemical tests for HH iron overload depend on the cut-off points used. The HEIRS study, which involved screening almost 100,000 participants for HH, concluded that TfS, a commonly used diagnostic test, has a low sensitivity and is highly biologically variable, thereby limiting its utility as a screening tool [43]. The authors also noted that whilst SF increases with iron overload, several other factors can also cause elevated SF levels, such as fatty liver and alcohol consumption, which decreases its sensitivity as a screening tool [43]. With regard to genotyping for C282Y homozygotes, a systematic review reported sensitivity ranged between 91.3% and 92.4%, and specificity between 98.8% and 100% [44].

Few studies have reported on adherence to HH treatment. In a workplace setting, compliance to treatment (TV) was reported to be 100% over a 12 month period [45]. However, a longitudinal study following participants over nine years reported that whilst adherence was high during the early stage of the study (80%), it decreased linearly to 33% in the ninth year [46].

Early symptoms of iron overload are vague and can be missed by physicians. A delay in diagnosis of HH could lead to end organ damage [27, 28]. Early detection and treatment of HH can improve clinical outcomes of patients with HH and result in normal life expectancy [47]. As such, strategies for early detection can reduce the burden of disease associated with HH. Different approaches have been suggested to increase the rate of early diagnosis, including enhanced training of physicians in combination with cascade screening and population screening. Whilst HH fulfils several of the criteria set out by the World Health Organization for diseases that may warrant population screening

programs [48], a lack of rigorous health economic evaluations to support efficient resource allocation has been cited as a barrier [29, 30, 41, 49].

To our knowledge, no comprehensive systematic reviews of health economic studies have been published on all approaches to HH screening programs or treatment. This study seeks to ascertain what economic evidence is available to support: 1. Population or targeted screening for HH; and 2. Treatment of HH.

2.4 Methods

The systematic review was performed using the Campbell and Cochrane Economics Methods Group (CCEMG) guidelines [50, 51]. Studies that included full or partial economic evaluations relating to HH were included. Full economic evaluations involve a comparison of the costs and consequences of two or more alternative interventions; partial economic evaluations involve examination of costs and/or consequences of either one or more interventions [52]. The target interventions were kept broad, allowing for inclusion of all possible screening and treatment studies. Studies using hypothetical populations in decision models were also included. No limits of language of publication were included. The only exclusion criteria were the absence of any health economic data reported within the publication or reviews of other work.

Information sources

Five health economic/economic databases- Centre for Reviews and Dissemination (CRD) including Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTAD) and NHS Economic Evaluation Database (NHSEED), Cost Effectiveness Analysis Registry (CEA Registry), and EconLit, and four biomedical databases - PubMed, Scopus, Embase (including Medline), and the Cochrane Collaboration were searched in June 2014 using a pre-defined search strategy detailed in Table 1. In addition, hand searching of citations from relevant papers, previous reviews and industry documents was performed. The search strategy comprised an abridged PICO standard (which references the participants, interventions, comparisons and outcomes), Medical Subject Headings (MeSH) terms and economic search filters. Following this initial search, review of title and abstract was conducted to finalise included studies.

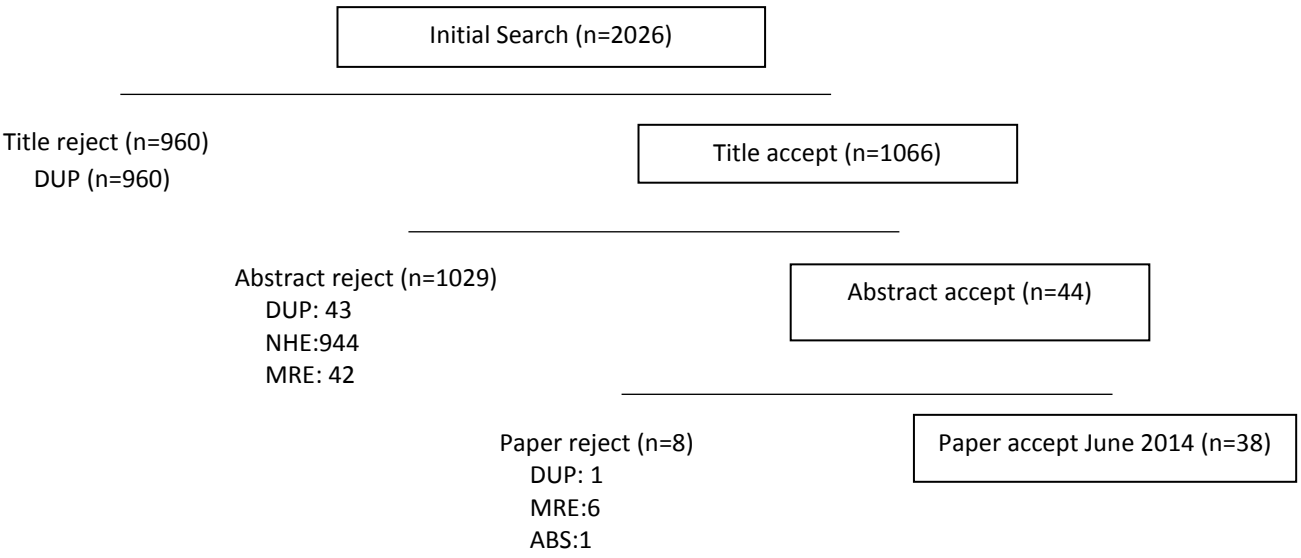
Table 1: Search strategy, conducted June 2014

Long Search	#1 AND #2 AND #3 NOT #4
#1 Economic filters (outcome)	"economic evaluation" OR cost OR effectiveness OR "cost effectiveness" OR "cost benefit" OR "cost analysis" OR "cost utility" OR CUA OR CBA OR CEA OR "health economic*" OR economic* OR "direct cost" OR "indirect cost" OR "intangible cost" OR "health care cost" in Title, Abstract or Keywords
#2 Participant	*haemochromatosis OR hemochromatosis OR "bronze diabetes" OR "iron overload" in Title, Abstract or Keywords*
#3 Intervention	*screening OR "health screening" OR prevention OR "early intervention" OR treatment OR prevent in Title, Abstract or Keywords*
#4 Excluding	*NOT animal in Title, Abstract or Keywords*
MeSH Search	(("Costs and Cost Analysis" explode all trees [Mesh] OR "Cost-Benefit Analysis" explode all trees [Mesh] OR "Cost of Illness" explode all trees [Mesh] OR "Cost Savings" explode all trees [MESH]) AND "Haemochromatosis" explode all trees [Mesh] OR "Hemochromatosis" explode all trees [Mesh])

Data collection process

Data were extracted on key parameters, including study design, sample size, duration of screening program, authorship, year of publication, country in which the study was conducted and study characteristics (screening parameters, setting, target group). Health economic metrics such as type of evaluation, year of assessment, currency, perspective, costs assessed, time frame, discount rate, methods for measuring and valuing outcomes and summary measure of efficiency calculated were recorded. Health economic studies were evaluated using the British Medical Journal Economic Evaluation Working Party (BMJ checklist) [53]. The BMJ checklist consists of 35-items, and a 36th item on generalizability. Each item was given a score: '1' if the item was performed, '0' if it was not and 'N/A' if the item was not applicable to the study. Equal weighting was given to each item. The number of '1' items was summed, and using the number of applicable items as the denominator the proportion was calculated, providing the final score as a percentage [54]. Studies were defined as low (<50%), moderate (50-75%) and high quality (>75%).

Figure 1: Flow diagram of study selection



2.5 Results

Study selection

A flow diagram of the search strategy is shown in Figure 1. The electronic search yielded 2,026 studies. Economic databases generated 34 studies (CRD, including DARE, HTAD and NHSEED (n=28), CEA Registry (n=4), and EconLit (n=2), and biomedical databases produced 1,992 studies, (PubMed (n=872), Scopus (n=643), Embase (including Medline; n=475), the Cochrane Collaboration (n=2)). After removal of duplicates, 1,066 studies were reviewed against the inclusion/exclusion criteria. 1,028 papers were excluded following screening of title and abstract. Papers that were excluded were neither partial nor full economic evaluations relating to HH. Thirty-eight studies met the inclusion criteria. Study selection was carried out by BdG and LS and data extraction conducted by BdG.

Characteristics of the Economic Analyses

Study Characteristics

Characteristics of the studies are presented in brief in Table 2 (and in detail in the appendix), grouped by intervention and methodological quality. Scores derived from the BMJ checklist are included in Table 2, however these should be interpreted with caution. The checklist is designed for authors to ensure they adhere to methodological requirements: it is not ideally suited to scoring the

robustness of the results of those papers. For example, with regard to the criterion on effectiveness, whilst a study may meet this criterion (i.e. stating the source of effectiveness data), the quality of this data is not captured by the checklist. Without proper consideration of the quality and appropriateness of the evidence and methodology employed, the robustness of results obtained remains uncertain. To balance this concern, the quality of the data that was used in economic evaluations will be discussed following a review of the more general characteristics of analyses.

Ten countries were represented: 11 studies originated from the US and seven from Canada. The remaining studies were from Germany, UK, Australia, the Netherlands, Norway, France, Switzerland and Italy. One paper was published in French, which was translated by AP. Publications spanned 25 years, from 1989 to 2014.

Of the 38 papers accepted, most examined costs associated with screening strategies (n=33); three reported costs associated with treatment for HH [55-57] and single papers reported on hospital costs associated with HH [58] and financial implications of allogeneic use of HH blood donations [59].

Table 2: Characteristics of studies

Screening studies (n=33)	Score (BMJ check-list)	Study design	Population	Screening strategies	Perspective	Outcomes
Categorised high quality (n=11); quality score >75%						
Rogowski, 2009 [68]	97%	Probabilistic decision analytic model, Markov modelling; CEA	Hypothetical cohort of 30year old male Caucasians	1. No screen; 2. Phenotype- *TfS x 2;* 3. Sequential- *elevated TfS and genotype;* 4. genotype- *C282Y* (all strategies are modelled for population (P) and cascade (C) screening separately)	Third party payer	No screen cf. strategy 3C= €41425; strategy 3P=€123996; strategy 4P=€161248
Gagne et al, 2007 [7]	94%	Computer simulation, decision model (decision tree); CEA	Hypothetical cohort from Quebec	165 algorithms of screening test, including phenotyping and genotyping	Health system	Cost saving: phenotype screen (LE=75.6, CAN$121) v. no screen v. (LE=68.6, CAN$143)
Bryant et al, 2009 [44]	94%	Decision analysis model (decision tree)	Hypothetical cohort: 45 year old male; family members	If raised TfS and SF: genotype v. liver biopsy: family: biochemical phenotype v. genotype	Health system	Genotyping v. liver biopsy for male= £216 saved/case detected. Biochemical v. genotyping for family =£7,982/case detected
Cooper et al, 2008 [60]	94%	Decision analysis model (decision tree); CEA	Hypothetical cohort: 45 year old male; family members	Confirmatory test: genotype v. liver biopsy	Government	£73,823 v. 83,068/case detected
Adams et al, 1995a [61]	88%	Decision analysis model (decision tree); CEA, CUA	Hypothetical cohort of blood donors and siblings	No screen v. phenotype *(UIBC, TfS, SF)*	Third party payer	$433,927 v. $307,567$/strategy for donors and siblings
Adams et al, 1995b [62]	88%	Decision analysis model (decision tree); CUA	Children of HMZ, aged 10-40years	No screen v. phenotype	Third party payer	Screening: $5,798/ HMZ identified; incremental cost savings:$12 at age 10, $65 at age 20, $245 at age 40
Stuhrmann et al, 2005 [69]	81%	Quasi-experimental; cost description	Health insurants	Genotype *PCR & restriction digest; 2 ASO methods; SPOLA; Microarray*	Third party payer	€11.20/test, €16.35/test, €13.79/test, €15.70/test
Hickman et al, 2000 [70]	81%	Quasi-experimental; cost description	Tertiary hospital patients	UIBC	Service provider	$2268.77/HH diagnosis
Adams & Valberg, 1999 [8]	78%	Decision analysis model (decision tree); CUA	Hypothetical cohort of voluntary blood donors and siblings of HMZ	No screen v. phenotype v. genotype	Third party payer	$0.97 v. $2.10 to -$178.00 (with varying cost of genotype test) (Incremental cost saving/person (c.f. no screen))
Phatak et al, 1994 [63]	78%	Decision analysis model (decision tree); CEA	Hypothetical cohort of 30 year old white males	No screen v. phenotype (TfS), liver biopsy	Societal	Cost saving
Patch et al, 2005 [39]	76%	Decision analysis model (decision tree); CEA; RCT	General practice patients	Phenotype (TfS) v. genotype	Government	£5.76 v. £9.43/person screened; £1440 v. £2358/HH case detected

Categorised moderate quality (n=10); quality score 50-75%						
Asberg et al, 2002 [32]	75%	Markov model; CUA	Hypothetical cohort of 1,000 males aged 30	No screen v. phenotype	Third party payer	Screening: $250/QALY
Vardarli* et al, 2009 [73]	71%	Quasi-experimental; CEA	Hospitalized diabetic patients	Sequential: *elevated ferritin, TfS,C282Y genotyping; elevated TfS, genotyping*	Third party payer	€15.60/pt & €4110/HH; €14.25/pt & €3754/HH
Schoffski et al, 2000 [64]	70%	Decision analysis model (decision tree); CEA	Hypothetical cohort of 25year old males	No screen v. genotype	Third party payer	Per person tested: €1.62 v. €7.26 LYG=€4441
Bassett et al, 1997 [65]	68%	Decision analysis model (decision tree); CEA	Hypothetical	Phenotype & liver biopsy v. phenotype, liver biopsy & cascade v. phenotype & genotype	Government	Screening with liver biopsy: $5,079-8,813/ HH identified Screening with genotyping: $3,954-4,410/ HH identified
Buffone & Beck, 1994 [67]	63%	Markov model; CEA	Hypothetical cohort of 25 year old males	No screen v. phenotype screen and treatment	Societal	$605/LYG
Smith et al, 1997 [74]	62%	Quasi-experimental; CEA	Workplace	Phenotype: *TfS; if elevated, fasting TfS, if elevated liver biopsy*	Third party payer	$90205/ program 39.32/screening $18,041/ HH
El-Serag et al, 2000 [88]	61%	Decision analysis model (decision tree); CEA	Siblings and children of probands	No screen v. phenotyping v. genotyping	Societal	Strategies ranged between $508-3665/LYG
Adams & Kertesz, 1992 [82]	55%	Quasi-experimental; cost analysis	Siblings of probands	Phenotype v. HLA typing	Third party payer	$1,150-1,450 v. $1,800-2,100 per (screening of a family of four)
Beutler & Gelbart, 2000 [83]	50%	Non-experimental, descriptive study; cost description	n/a	Genotyping	Laboratory	$8.62/test
Ropert-Bouchet, 2012 [84]	50%	Non-experimental, descriptive study; cost description	People with HH	n/a	Third party payer	n/a
Categorised low quality (n=12); quality score <50%						
Barton et al, 2002 [75]	44%	Quasi-experimental; CEA	Workplace	Phenotype	Third party payer	$8,826/HH identified
Adams, 1998 [76]	42%	Quasi-experimental; CEA	Children of HMZ	Phenotype v. spousal genotyping	Health service	$58,200 v. $35,600/strategy
Jacobs et al, 2005 [77]	40%	quasi-experimental; CEA	Hospital inpatients	No screening guideline v. sequential	Third party payer	€2380 v. €2600 (per HH diagnosis pre and post guideline implementation)
Stave et al, 1999 [71]	36%	Quasi-experimental; cost description	Workplace	Phenotype	Third party payer	$27850/program
Bhavnani et al, 2000 [78]	35%	Quasi-experimental; CEA	Blood samples from hospital inpatients, outpatients and GP patients	Sequential *(phenotype followed by genotype)*	Laboratory	£117/HH identified
Asberg et al, 2001 [42]	32%	Quasi-experimental; CEA	General population aged ≥20 years	Sequential	Third party payer	$390/HH identified

Baer et al, 1995 [79]	29%	Quasi-experimental; CEA	Community health centre; males aged ≥30years	Phenotype	Third party payer	$65,000/HH identified
Adams et al, 2000 [80]	22%	Quasi-experimental; CEA	Voluntary blood donors	Phenotype (x2) v. genotype UIBC; TfS	Service provider	UIBC $5,570/HMZ identified
Lederle, 1989 [85]	22%	Non-experimental; cost description	n/a	Phenotype	n/s	$24,804/HH diagnosis
Balan et al, 1994 [81]	15%	Quasi-experimental; CEA	Community health centre	Phenotype	Service provider	$5,631-8,447/HH identified
Timms et al, 2002 [72]	5%	Quasi-experimental; cost description	Community-based patients diagnosed with chondrocalcinosis	Genotype: PCR/SSP & PCR/RFLP	Service provider	£1/test; £64/HH
Delaveyne et al, 2004* [89]	-	Abstract of CEA; model	Population screening v. family screening	SF and TfS with confirmatory genotyping for C282Y.	n/s	€3.6-19.5 million v. €78,000 (per program)
Treatment and other studies (n=5)						
Rombout-Sestrienkova et al, 2012 [55]	79%	RCT; cost analysis	Newly diagnosed HH patients	Treatment: phlebotomy v. erythrocytapheresis	Societal	€71.49 v. €251.18 (per procedure); €4438 v. €3005
Mariani et al, 2005 [56]	53%	Non-experimental-descriptive, case series; cost analysis	Patients with severe HH	Treatment: erythrocytapheresis plus erythropoietin v. phlebotomy	Service provider	€602 v. €35 (Total mean costs)
Stefashyna et al, 2014 [57]	38%	Quasi-experimental; cost analysis	Volunteer blood donors	whole blood donation v. double-erythrocytapheresis	Service provider	USD186 v. 238, but fewer treatments required for latter.
Gribble et al, 2009 [59]	38%	Non-experimental; cost description	HH blood donors	n/a	Service provider	$6000 v. $20345
Dye et al, 2011 [58]	n/a	Non-experimental, cost analysis	Hospital morbidity data system	n/a	Service provider	$21,349, $2,827

Note: * abstract only; ~ refers to prevalence of HH and suspected iron overload in population; Cost saving refers to total cost of caring for a HMZ with no screening minus the total cost of screening, calculated for a range of ages.

ASO allele-specific oligonucleotide; CEA cost effectiveness analysis; CUA cost utility analysis; HMZ homozygote; LYG Life Year gained; n/a not applicable; n/s not stated; PCR polymerase chain reaction; RFLP restriction fragment length polymorphism; SF serum ferritin; Sfe serum iron; SPOLA Solid-phase oligonucleotide ligation assay; SSP sequence specific primers; TfS Transferrin saturation; UIBC unsaturated

Screening

Of the 22 screening studies, most were quasi-experimental; and almost half (n=14) employed some form of modelling. The quasi-experimental studies usually incorporated a cost-effectiveness analysis; most modelled studies used decision modelling techniques, most commonly a simple decision tree (n=11) [7, 8, 39, 44, 60-66]. In addition, three studies employed Markov modelling [32, 67, 68]. Other studies were a combination of quasi-experimental and cost description [69-72], quasi-experimental and cost effectiveness analysis [42, 73-81], quasi-experimental and cost analysis [82]. There were three non-experimental studies including a cost description [83-85].

The economic perspective of the screening studies was reported as third party payer in 48% of studies [8, 32, 42, 61, 68, 69, 71, 73-75, 77, 79, 82, 84, 86, 87]; service provider in 12% [72, 76, 80, 81]; societal [37, 67, 88], government [39, 60, 65] and pathology laboratory [70, 78, 83] in 9% respectively and health system in 6% [7, 44]. Perspective was not evident in 6% [85, 89]. All screening papers reported direct costs only. Unit costs were sourced from government reimbursement rates in 19% [7, 32, 42, 65, 68, 88], national/local set/benchmarked prices [39, 44, 60, 70] or laboratory prices [77, 83, 88] in 9% respectively, health insurance companies [74, 75] in 6%, and hospital costs [63], laboratory supplier [69] or from an organisation representing medical specialists [88] in 3% of studies respectively. The source of cost data was not reported in 50% (n=16) [8, 61, 62, 64, 67, 71-73, 76, 78-82, 85, 89].

The majority of studies that used decision analysis methods (n=14) modelled screening programs over lifetime (71%) [7, 8, 32, 61-64, 67, 68, 88]. A single modelled study had a time horizon of <1 year [39], and in four modelling studies the time horizon was either unclear or not stated [44, 60, 65, 89]. Most quasi-experimental studies used a time horizon of ≤1 year [69-71, 73, 78, 79], and single studies used a time horizon of two [42], four [77], five [82] and 11.5 years [75] respectively. In four quasi-experimental studies the time horizon was not stated [72, 74, 76, 80]. Of the three non-experimental studies, two used a time horizon of one year or less [83, 85] and one study did not report this [84].

Discount rates were reported in 46% of studies in which this was applicable, most commonly 3% annually [55, 61-63, 68, 88]. These studies originated from the USA [63, 88], Canada [8, 61, 62] and Germany [68]. A second German study employed differential discounting, using 5% for costs and 0% for effectiveness [64]. No discounting of costs or consequences was reported in 46% of screening

studies which may have methodologically benefitted from this [7, 32, 39, 60, 75, 84]. The remaining studies did not discount costs or consequences as the timeframe of the study did not warrant this, i.e. less than 12 months' time horizon.

Treatment and other economic papers

Five studies were identified that reported other economic aspects of HH. All studies reported direct costs only, with the exception of Rombout-Sestrienkova, who reported both direct and indirect costs [55]. Two of the treatment papers reported on studies of a duration greater than one year [55, 57] and the third study did not provide a timeframe. No treatment studies reported discounting costs or effects.

Studies compared costs between TV and erythrocytapheresis [55], [57], and erythrocytapheresis and erythropoietin in comparison with TV [56]. The latter was a case study of three patients, which provided clear details regarding the treatment regimen. Of the two studies comparing TV and erythrocytapheresis, one was an RCT with a well-defined protocol, which, whilst underpowered, provided a useful approach to compare treatment arms [55]. The final study was observational and had several methodological shortcomings which limited the validity of the findings [57].

A further two papers were identified that examined other economic aspects related to HH. Gribble and colleagues examined the effect of a potential Food and Drug Administration (FDA) variation on use of HH donated blood for allogeneic purposes in the US [59]. Another study was identified that reported costs associated with hospitalisation of HH patients in an Australian jurisdiction [58].

Methodological assessment

The overall mean quality score of studies was 57.9% (SD=24.6). For screening studies, eleven were high quality (33%), ten moderate quality (30%), and 36% (n=12) were low quality. The mean quality score of the three treatment papers was 56.58% (SD=21.1), and the two papers reporting other economic aspects of HH returned a mean quality score of 47.0% (SD=12.0)

Synthesis of results

Screening

Table 2 displays a summary of the study characteristics of the papers, with the full summary in the appendix. A large degree of heterogeneity between the studies was identified, in respect to

estimates of prevalence, penetrance, uptake of screening, screening approaches, phenotypic thresholds, target populations, perspective of the economic analyses and country. Systematic reviews that identify studies with a large degree of heterogeneity should not involve a meta-analysis of the data [90]. A narrative synthesis was therefore undertaken, employing the approach outlined by Popay and colleagues [91].

Whilst the majority of studies reported both phenotypic and genotypic screening programs to be cost-effective, the evidence regarding effectiveness was of low quality in some studies. Effectiveness of screening programs can be measured through uptake of screening amongst the target population, adherence to treatment and number of cases detected. These estimates are, in turn, dependent upon prevalence and penetrance estimates.

Both prevalence and penetrance estimates for HH are highly variable and difficult to precisely ascertain, which necessarily increases uncertainty in modelled studies. The modelled studies considered in this review used population prevalence estimates for C282Y homozygosity ranging between 0.2% and 0.7% for persons of northern European heritage [7, 8, 32, 44, 60-65, 67, 68]. A small number of studies employed sensitivity analyses around prevalence estimates [7, 63, 68, 89], which were similar to recent epidemiological estimates of C282Y homozygosity of between 0.44% and 0.68% amongst persons of northern European heritage [11, 13]. Clinical penetrance rates were highly variable, in part due to different definitions of penetrance being employed. Regarding C282Y homozygotes, estimates for males ranged between 0.035 and 0.76 [7, 8, 32, 44, 60-64, 66-68] and for females 0.28 and 0.32 [8, 44, 60-62].

Uptake of population screening programs was either not considered or considered to be absolute in almost all models [7, 8, 32, 44, 60-67]. Where probability estimates of uptake of screening were reported, these varied considerably. Estimates were highest amongst voluntary blood donors (0.97) [80], a workplace (0.85) [75] and a general Norwegian population (0.70) [42]. More conservative estimates were used for German health insurants (~0.003) [69], and from a UK RCT (0.32) [39]. One study assumed the probability of interest in population screening to be 0.805, and of this group, an uptake rate of 0.058. Adherence to treatment was only considered in five modelled studies. Four of these used estimates of between 80% and 90% [32, 61, 62, 64], whilst a fifth used a more conservative estimate of 33% [68]. According to the author of this latter study, the use of this lower

estimate was based on the commonly used assumption of 50% for adherence to drug treatment, and that a lower rate for more demanding interventions should be used.

The screening strategies that were examined included biochemical phenotype (serum ferritin, transferrin saturation, unsaturated iron binding capacity, alanine transaminase), biochemical phenotype with confirmatory liver biopsy, genotype and sequential (combination of both phenotype and genotype or different phases for biochemical tests). The approaches to screening varied considerably, particularly for biochemical investigations (see Table 3). Genotyping was used to confirm a diagnosis of HH in most studies published after 1999, i.e. following the identification of the HFE mutation [4].

For iron studies, the cut-off points used to indicate iron overload and/or a diagnosis of HH varied: TfS for mixed cohorts ranged between ≥45-60% [39, 44, 65, 73, 74, 77, 78, 80, 92], ≥50-55% for females [7, 8, 42, 61, 62, 71, 75, 76] and ≥55-60% for males [7, 8, 42, 61-63, 71, 75, 76, 79]. The cut-off points for SF were <110µg/l - 300 µg/l for females [7, 8, 44, 71, 75, 82]; 200µg/l-500µg/l for males [7, 8, 71, 75, 79, 82] and 280-400µg/l for a mixed cohort [77]. HFE genotyping was conducted for either C282Y [8, 44, 60, 64, 68, 69, 73, 76, 80, 89] or both C282Y and H63D mutations [7, 72, 78, 88, 93, 94] .

The heterogeneity of biochemical testing approaches makes comparison across studies not possible. Whilst TfS and SF were commonly used in economic evaluations of screening, investigators from the HEIRS study found that non-fasting and fasting TfS and SF were not ideally suited to this task [27]. Genotyping was included in most evaluations following the development of the test for the mutation of the HFE gene. In a systematic review, sensitivity of the C282Y genotype test was reported to range between 91.3% and 92.4%, and specificity between 98.8% and 100% [44], making this a more effective test for HH screening.

Assumptions regarding prevalence, penetrance, sensitivity and specificity of tests, uptake of screening and adherence to treatment were highly variable across modelled studies, reflecting the paucity of robust data in the earlier years of economic analysis of HH-related interventions. However, more reliable probability estimates taken from epidemiological studies have improved the validity of recent CE models.

Table 3: Biochemical phenotype screening approaches

Approach to biochemical phenotype screening	Number of studies
TfS (non-fasting) followed by TfS (fasting), SF [8, 32, 37, 42, 62, 65, 67]	7
TfS followed by genotype [65, 68]	2
TfS [80, 88]	2
TfS (non-fasting) [39, 65]	2
TfS (non-fasting) followed by TfS (fasting) [74]	1
TfS, SF followed by TFS, SF˜ [77]	1
TfS followed by TfS [68]	1
TFS (fasting followed by TFS, SF, FBC, AST, ALT (fasting) [79]	1
UIBC followed by TfS followed by SF [61]	1
ALT followed by TfS & SF followed by SF followed by genotype [78]	1
UIBC [80]	1
UIBC followed by TfS [7]	1
UIBC followed by genotype [7]	1
UIBC followed by TFS followed by SF, genotype [70]	1
SI [88]	1
SI, TfS (fasting) followed by SF [76]	1
SI (fasting) followed by SI, TIBC, SF* [92]	1
TfS followed by UIBC [7]	1
TI followed by SF [71]	1

Note: Studies reported multiple screening strategies; sequential testing is carried out when the initial test result is elevated
* The second stage of testing is conducted on the initial blood sample but in a different laboratory
˜ One of these tests is conducted after over fasting
Gagne et al investigated 165 screening algorithms. Only the three most cost-effective are included in this table.
Abbreviations: TfS: Transferrin saturation, SF: serum ferritin; UIBC: Unsaturated iron binding capacity; SI: serum iron; ALT: alanine transaminase; TI: Transferrin index

Utilities

All four of the CUA studies on screening [8, 61, 62, 95] assigned utility weights for cirrhosis, diabetes, heart failure and/or combinations of these, however the source of these weights was not stated. Adams and colleagues did not report the utility weight used for other states, i.e. homozygotes with no clinical symptoms of iron overload-related conditions [8, 61, 62]. Asberg and colleagues assumed a basal utility weight of 1.00 for all HH conditions, with the exception of cirrhotic patients, who were assigned a value of 0.95 [95], notably higher than published elsewhere. Uhlig and colleagues reported a mean utility measure for the Norwegian population using the SF-6D of 0.803 [96]. Dan and colleagues measured the utilities of US patients with cirrhosis and reported a utility of 0.64 using the SF-6D [97]. Similarly, two studies by Adams and colleagues used utility values of 0.8 for symptoms of cirrhosis, 0.9 for diabetes and 0.5 for heart failure (the third study did not report the values used [61]). In contrast to these estimates, Fryback and colleagues published utility population norms for the US [98]. Using the SF-6D, mean population norms for persons aged 35-74 ranged between 0.79 and 0.81, and using the EQ-5D, ranged between 0.87 and 0.89. This suggests that, with the possible exception of heart failure, Adams' estimated utility weights were higher than would be

expected if participants' utility scores were measured directly; and the potential utility gains underestimated. Of note, none of the studies incorporated utility weights associated with arthritis. Adams and Speechley found that amongst a small sample of HH patients, arthritis strongly affected quality of life, more so than cirrhosis and diabetes [99]. Consequently, CUA studies that do not include utility weights associated with arthritis may be under-estimating the impact this condition has on overall health associated with HH.

Treatment and other studies

This review identified three economic evaluations of HH treatment. Two of these studies concluded that TV was a more cost-effective strategy than erythrocytapheresis [55] and erythrocytapheresis plus erythropoietin [56]. The third study did not find double-erythrocytapheresis to be superior to TV from a cost perspective [57].

Costs of other aspects of HH were assessed in two partial economic analyses. The first was a cost description study which assessed hospital costs [58]. The authors reported that between 2000 and 2006, disorders of iron metabolism cost USD2,828 per admission (2007/08 USD).

The second study was a cost analysis assessing potential revenue earned from a policy variance allowing for red blood cell (RBC) product to be sourced from HH venesected blood [59]. When comparing loss of revenue from provision of free venepuncture services to HH patients with potential revenue from collection of RBC units, a favourable financial outcome was identified

2.6 Discussion

To date, this is the first comprehensive systematic review of health economic studies of all aspects of HH screening and treatment. To our knowledge, just one other systematic review of health economic evidence and genetic screening has considered HH. This review assessed the economic evidence for screening a range of disorders, one of which was HH [100]. Our current review critically appraises all full and partial economic evaluations of genetic and phenotypic screening programs and treatment approaches for HH. A meta-analysis was not possible due to the high degree of heterogeneity between the studies.

Screening

Whilst almost all studies evaluating any form of screening program in comparison with no screening concluded screening to be cost effective [32, 64, 67, 88] or cost saving [7, 8, 61-63], methodological limitations undermine the robustness of these results. In cost effectiveness studies the assessment of effectiveness is the crucial first step [52]. A paucity of effectiveness data (prevalence, penetrance, uptake of screening and adherence to treatment), particularly in studies conducted prior to 2000, contributed to the use of highly variable estimates in modelled studies. As the body of HH literature has grown considerably in the past decade, the quality of data used to populate economic models of HH interventions has improved.

In modelling studies using more than 150 algorithms, Gagne and colleagues found that clinical penetrance rates had a large effect on the assessment of cost effectiveness [7]. Penetrance rates are subject to more variability than prevalence, in part due to different definitions of penetrance: ranging from elevated iron studies to life threatening comorbidities related to iron overload. The European Assoication for the Study of the Liver (EASL) identified this inconsistency in 2000 and recommended use of four distinct categories of HH, ranging from genetic mutation only, through to organ damage [29]. A recent Australian epidemiological study reported penetrance (including early symptoms such as arthritis of the metacarpophalangeal joints through to irreversible organ damage) as 28.4% for males and 1.2% for females [11]. Penetrance of cirrhosis amongst C282Y homozygotes has been reported by several studies, with estimates ranging between 2% and 6% [11, 38, 42]. Earlier studies included in this review used markedly higher rates for developing life-threatening disease manifestations (commonly described as cirrhois and heart disease): 40 to 76% for males and 28 to 32% for females [8, 61, 62, 67]. More recent studies have used lower estimates ranging between 1.6% to 5.6% [7, 68] that are in-keeping with recent epidemiological data.

An important aspect to consider regarding economic implications of a large-scale screening program is uptake of screening. Whilst many modelled studies did not consider this, so implicitly assumed 100% uptake, amongst those that did, estimates were variable, as were the study populations considered. Amongst voluntary blood donors, an uptake rate of 97% was used [80], 85% for a US workplace [75] and 70% for the general population of a Norwegian county [42]. These latter two studies used estimates based on clinical studies in which a broad range of health interventions were offered, not just HH screening. It is likely that this broad range of interventions enhanced uptake more so than if HH screening was offered on its own. In support of this, far lower rates were

reported for German health insurants (0.3%) [69] and from a UK general practice setting (32%) [39] for HH-only screening. One study assumed a probability of interest in screening for the German male population screening of 5.8%, and of this group, an uptake rate of 80.5% [68].

Adherence to treatment is another important aspect of the cost effectiveness of HH screening programs. Both treatment costs and disease-related costs when treatment is not adhered to, impact significantly on effectiveness and long-term costs [68]. Of the five studies that considered adherence, four of these used estimates of between 80 and 90% [32, 61, 62], and the fifth used an estimate of 33% [68]. This latter estimate was based on the commonly used assumption of 50% for adherence to drug treatment, and that a lower rate for more demanding interventions should be used [68]. In addition, a longitudinal study of HH treatment noted a linear decrease in adherence from 80% to 33% by year nine [46]. This suggests that the assumptions regarding adherence in earlier studies was highly optimistic, potentially increasing the cost-effectiveness of screening interventions.

Whilst assumptions are necessary when calculating the cost-effectiveness of HH screening programs, these have generated uncertainty regarding the findings. This is understandably more of an issue amongst studies that were conducted when little data was available regarding key parameters. However, of the more recent studies published, Rogowski's economic analysis was the only one to be based on an objective assessment of the effectiveness of screening. Many of the studies contained in this review, particularly the early studies, contain assumptions that cannot be supported and may lead to incorrect conclusions being drawn as to the cost-effectiveness of screening.

Almost all of the modelled studies employed decision analysis techniques using decision trees, with short time-horizons (i.e one year or less). The nature of HH, whether treated or not, is one which affects the patient for their lifetime, therefore to fully capture the costs and effects, models should ideally be conducted over a lifetime. Further, models would use probabilistic decision analysis to incorporate uncertainty of key parameters, and Markov modelling to capture long-term costs and effects. Just one paper did this [68], and two used decision trees and Markov modelling [32, 67].

Whilst targeted screening of individuals at high risk of HH and iron overload (i.e. offspring and siblings of HH probands) has been adopted by many governments and is viewed as a cost effective

approach, questions remain regarding the cost effectiveness of population screening. In the current review, just one paper was identified that reported population screening to be not cost effective [68]. This study by Rogowski was of very high quality according to the BMJ checklist, and is the highest quality cost effectiveness study of HH screening to date.

Rogowski's modelled study aimed to calculate the cost effectiveness of three screening strategies (genotypic, phenotypic and sequential) for the German Caucasian male population aged 30 years and male offspring of HH probands. This model assumed that genetically HH positive people '*with elevated serum iron values would be offered phlebotomies; [and] annual serum iron testing would be offered to all others*'. Rogowski does not provide a definition of 'elevated' serum iron values, which is in keeping with the EASL guidelines. These guidelines make note of the fact that internationally, recommendations regarding commencement of TV are based on empirical evidence, making it unclear when treatment should commence. Different cut-off points indicative of iron overload and the consequential need for treatment will necessarily alter the number of participants requiring treatment, and therefore the costs associated with the strategy. Again in accordance with EASL guidelines, the study assumed annual SF monitoring for C282Y homozygotes who do not have elevated serum iron levels at the time of diagnosis. The study concluded that targeted sequential screening of male offspring was the most cost-effective strategy.

Annual SF monitoring for C282Y homozygotes who do not have elevated serum iron levels at the time of diagnosis whilst in accordance with EASL guidelines, is not a universal strategy. For example countries such as Australia recommend retesting every two to five years [15]. Further, Adams and Barton note longitudinal studies of patients with HH suggest that many HH probands will not develop iron overload, thereby rendering annual iron studies excessive [101]. As such, there may be an overestimation of costs in the screening arm of Rogowski's model and the impact of alternative strategies is appropriate.

Utilities

Another aspect of economic evaluations that requires further attention in the future are the utility weights included. To-date, no studies have used reliable utility weights when conducting CUA of HH screening programs. The four studies identified in this review used estimates of unknown source that were likely to be higher than expected if measured directly from a sample of HH patients [8, 32,

61, 62]. Potential utility gains could be grossly underestimated. More research investigating utility weights for the various stages of HH would contribute to more robust cost utility analyses.

The penetrance estimates used in Adams' three studies for life-threatening conditions (heart failure, cirrhosis, hepatocellular carcinoma and diabetes) were 0.43 for males and 0.28 for females. Asberg and colleagues (2002) defined penetrance as cirrhosis, and used a probability estimate of 0.049. The estimates used by Adams and colleagues are higher than found in recent epidemiological data, noted above, whereas Asberg's is within the range reported. Adam's utility estimates for each condition were found to be higher for most conditions than reported in the literature [102-104], as were the penetrance estimates. The use of these inflated estimates is likely to lead to incorrect results. Whilst Asberg used a penetrance estimate that was in keeping with recent epidemiological data, which ranges between 0.02 and 0.06 [11, 38, 42], the utility score of 0.95 assigned to this state is notably higher than reported for non-HH patients with cirrhosis (ranging between 0.67 and 0.75) [102].

The HSUVs incorporated into the economic evaluations reviewed focused on cirrhosis, type 2 diabetes and heart disease. Other health conditions/states, such as fatigue and arthritis, were not considered. In part, this may have been due to uncertainty surrounding the aetiology and the subjective measurement of these conditions. However, relatively high rates of HH-related osteoarthritis have been reported [105-107], and quality of life amongst HH patients has been found to be more negatively impacted upon by arthritis than cirrhosis or diabetes [99]. Therefore, ignoring utility estimates related to arthritis may underestimate utility gains from HH interventions. With care, HSUV for a range of health states related to HH should be included in CUA, with the net effect of multiple morbidities preferably captured via a validated multi-attribute utility instrument.

One of the strengths of this review was there were no limitations on language or date of publication. Although a meta-analysis was not possible, it is clear that whilst most full economic evaluations reported HH screening programs to be cost effective or cost-saving, there were methodological limitations in these studies that impact the robustness of the findings. Further rigorous, full economic evaluations are required to resolve some of the controversies regarding the economic aspects of screening programs. More robust modelling, incorporating a more complete understanding of the costs associated with HH and accurate utility weights, will make a valuable contribution to this debate.

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Appendix 2B Table 1: Characteristics of the studies

Table 2: Characteristics of studies

Screening studies (n=32)	Score (BMJ check-list)	Origin	Study design	Population	Partic-ipants *n*	Control	Screening strategies	Pheno-type cut-off points	Genotype	Model probability assumptions	Costs included	Time horizon	Discount rate	Perspective	Outcomes
Categorised high quality (n=11); quality score >75%															
Rogowski, 2009 [68]	97%	Germany	Probabilistic decision analytic model, Markov modelling; CEA	Hypothetical cohort of 30year old male Caucasians	n/a	yes, *n/a*	1. No screen; 2. Phenotype- *TfS x 2;* 3. Sequential- *elevated TfS and genotype;* 4. genotype- *C282Y* (all strategies are modelled for population (P) and cascade (C) screening separately)	n/s	C282Y HMZ	PR=0.004 PE=0.035 U=0.805 (of 0.058 of population who are interested) A=0.33	Printed material, DNA tests, ambulatory care (reimbursement rates), incurred for cirrhosis	Lifetime	3%	Third party payer	No screen cf. strategy 3C= €41425; strategy 3P=€123996; strategy 4P=€161248
Gagne et al, 2007 [7]	94%	Canada	Computer simulation, decision model (decision tree); CEA	Hypothetical cohort from Quebec	1 million	yes, n/a	165 algorithms of screening test, including phenotyping and genotyping	Multiple	C282Y and H63D combined genotypes	PR= 0.002 C282YHMZ, 0.024 compound HTZ PE=0.05-0.9 C282YHMZ, 0.005 U=n/r A=n/r	Multiple medical services, blood tests, treatments for HH, cirrhosis, diabetes, cardiomyopathy, liver biopsy	Lifetime	Not conducted	Health system	Cost saving: phenotype screen (LE=75.6, CAN$121) v. no screen v. (LE=68.6, CAN$143)
Bryant et al, 2009 [44]	94%	UK	Decision analysis model (decision tree)	Hypothetical cohort: 45 year old male; family members	n/a	yes, n/a	If raised TfS and SF: genotype v. liver biopsy: family: biochemical phenotype v. genotype	TfS>45%, SF>300 µg/l	C282Y HMZ	PR=0.038 PE= 0.76 ♂ and 0.32 ♀ U=n/r A=n/a	DNA test, biochemical tests, TV, liver biopsy, health appts	Testing and treatment period	n/a	Health system	Genotyping v. liver biopsy for male= £216 saved/case detected. Biochemical v. genotyping for family =£7,982/case detected
Cooper et al, 2008 [60]	94%	UK	Decision analysis model (decision tree); CEA	Hypothetical cohort: 45 year old male; family members	n/a	yes, n/a	Confirmatory test: genotype v. liver biopsy	n/a	C282Y HMZ	PR=0.0038˜ PE= 0.76 ♂ and 0.32 ♀ U=n/r	DNA test, biochemical tests, TV, liver biopsy, health appts	Testing and treatment period	n/a	Government	£73,823 v. 83,068/case detected

Appendix 2B Table 1: Characteristics of the studies

									A=n/a						
Adams et al, 1995a [61]	88%	Canada	Decision analysis model (decision tree); CEA, CUA	Hypothetical cohort of blood donors and siblings	10,000	yes, n/a	No screen v. phenotype *(UIBC, TfS, SF)*	TfS<50% for ♀ and >60% for ♂	n/a	PR=0.003 PE: life-threatening disease 0.43 ♂ and 0.28 ♀ U=n/r A=0.8	Blood tests, HLA typing, TV, liver biopsy with and without complications, treatments for heart failure, cirrhosis (ambulatory and hospital), diabetes, medical consultations	Lifetime	3%	Third party payer	$433,927 v. $307,567$/strategy for donors and siblings
Adams et al, 1995b [62]	88%	Canada	Decision analysis model (decision tree); CUA	Children of HMZ, aged 10-40years	255	n/a	No screen v. phenotype	TfS<55% for ♀ and >60% for ♂		PR=0.003 HMZ, 0.010HTZ PE: life-threatening disease 0.43 ♂ and 0.28 ♀ U=n/r A=0.9	Treatments for heart failure, cirrhosis, hepatocellular carcinoma, diabetes	Lifetime	3%	Third party payer	Screening: $5,798/ HMZ identified; incremental cost savings:$12 at age 10, $65 at age 20, $245 at age 40
Stuhrmann et al, 2005 [69]	81%	Germany	Quasi-experimental; cost description	Health insurants	3930	n/a	Genotype *PCR & restriction digest; 2 ASO methods; SPOLA; Microarray*	n/a	C282Y HMZ	n/a	DNA test kit, personnel time, filter paper, postage	Present	n/a	Third party payer	€11.20/test €16.35/test €13.79/test €15.70/test
Hickman et al, 2000 [70]	81%	Australia	Quasi-experimental; cost description	Tertiary hospital patients	5182	n/a	UIBC	<30µmol/l	C282Y HMZ	n/a	Laboratory testing: UIBC, TfS	Present	n/a	Service provider	$2268.77/HH diagnosis
Adams & Valberg, 1999 [8]	78%	Canada	Decision analysis model (decision tree); CUA	Hypothetical cohort of voluntary blood donors and siblings of HMZ	10,000 & 50	n/a	No screen v. phenotype v. genotype	TfS<50% for ♀ and >60% for ♂; SF<150µg/l for ♀ and >200µg/l for ♂	C282Y HMZ	PR=0.003 PE: life-threatening disease 0.43 ♂ and 0.28 ♀ U=n/r A=n/r	Treatments for heart failure, cirrhosis, hepatocellular carcinoma, diabetes, blood collection fee, testing, staffing	Lifetime	3%	Third party payer	$0.97 v. $2.10 to -$178.00 (with varying cost of genotype test) (Incremental cost saving/person (c.f. no screen))
Phatak et al, 1994 [63]	78%	US	Decision analysis model (decision tree); CEA	Hypothetical cohort of 30 year old white males	n/a	yes, n/a	No screen v. phenotype (TfS), liver biopsy	55%	n/a	PR=0.003 PE=0.5 U=n/r A=n/r	Blood tests, liver biopsy, TV, liver MRI, treatment for hepatocellular carcinoma, diabetes,	Lifetime	3%	Societal	Cost saving

Appendix 2B Table 1: Characteristics of the studies

											heart failure, liver transplantation				
Patch et al, 2005 [39]	76%	UK	Decision analysis model (decision tree); CEA; RCT	General practice patients	502 (phenotype arm); 574 (genotype arm)	n/a	Phenotype (TfS) v. genotype	≥45%	C282Y HMZ and C282Y/H63D heterozygotes	PR=n/a PE=n/a U=0.32 A=n/a	Invitation to screening, sample packs and handling, consumables, blood tests and analysis, medical consultation	Current	n/a	Government	£5.76 v. £9.43/person screened; £1440 v. £2358/HH case detected
Categorised moderate quality (n=10); quality score 50-75%															
Asberg et al, 2002 [32]	75%	Norway	Markov model; CUA	Hypothetical cohort of 1,000 males aged 30	n/a	n/a	No screen v. phenotype	n/s	n/a	PR=0.007 EAMR (cirrhosis) =0.049 U=n/r A=0.8	Reagent costs for blood tests at first and second screening, medical consultation, liver biopsy	Lifetime	n/s	Third party payer	Screening: $250/QALY
Vardarli* et al, 2009 [73]	71%	Germany	Quasi-experimental; CEA	Hospitalized diabetic patients	527	n/a	Sequential: *elevated ferritin, TfS,C282Y genotyping; elevated TfS, genotyping*	TfS>45% Ferritin n/s	C282Y HMZ	n/a	Reagents and staff time	Present	n/a	Third party payer	€15.60/pt & €4110/HH; €14.25/pt & €3754/HH
Schoffski et al, 2000 [64]	70%	Germany	Decision analysis model (decision tree); CEA	Hypothetical cohort of 25year old males	n/a	yes, n/a	No screen v. genotype	n/a	C282Y HMZ	PR=0.0025 PE=0.1 U=n/r A=0.9	DNA test, TV, treatments diabetes, cirrhosis, cardiomyopathy, heart failure, liver transplantation and follow-up care	Lifetime	5% for costs, 0% effects	Third party payer	Per person tested: €1.62 v. €7.26 LYG=€4441
Bassett et al, 1997 [65]	68%	Australia	Decision analysis model (decision tree); CEA	Hypothetical	n/a	n/a	Phenotype & liver biopsy v. phenotype, liver biopsy & cascade v. phenotype & genotype	TfS ≥45%, 55%	C282Y HMZ	PR=0.0036 PE=n/r U=n/r A=n/a	Blood tests: initial and repeat, medical consultations	n/s	n/s	Government	Screening with liver biopsy: $5,079-8,813/ HH identified Screening with genotyping: $3,954-4,410/ HH identified
Buffone & Beck, 1994 [67]	63%	US	Markov model; CEA	Hypothetical cohort of 25 year old males	n/a	n/a	No screen v. phenotype screen and treatment	n/s	n/a	PR=0.003 PE=0.4-0.5 U=n/r A=n/r	Blood tests, liver biopsy, TV, treatment for disease	Lifetime	Not performed	Societal	$605/LYG
Smith et al, 1997 [74]	62%	US	Quasi-experimental; CEA	Workplace	2294	n/a	Phenotype: *TfS; if elevated, fasting*	TfS>55% or TfS >45% & SF >300ng/ml for	n/a	n/a	Blood tests: initial and repeated, general and	Present	n/a	Third party payer	$90205/ program 39.32/screening $18,041/ HH

Appendix 2B Table 1: Characteristics of the studies

							TfS, if elevated liver biopsy	♀ and >400ng/ml for ♂			specialist medical consultations, administrative costs of screening program				
El-Serag et al, 2000 [88]	61%	US	Decision analysis model (decision tree); CEA	Siblings and children of probands	n/a	n/a	No screen v. phenotyping v. genotyping	n/s	C282Y HMZ and heterozygotes	PR=0.1 (HTZ) PE: cirrhosis=0.3, type 2 diabetes=0.2. heart failure=0.05 U=n/r A=n/r	DNA and blood tests, TV, treatment for cirrhosis, diabetes, hepatocellular carcinoma, heart failure	Lifetime (from age 10 for children and age 45 for siblings of probands	3%	Societal	Strategies ranged between $508-3665/LYG
Adams & Kertesz, 1992 [82]	55%	Canada	Quasi-experimental; cost analysis	Siblings of probands	105	n/a	Phenotype v. HLA typing	SF: >200µg/l for ♀, >350µg/l for ♂; TfS>55%	n/a	n/a	HLA typing, blood tests, medical consultation, liver biopsy	5yrs	n/s	Third party payer	$1,150-1,450 v. $1,800-2,100 per (screening of a family of four)
Beutler & Gelbart, 2000 [83]	50%	US	Non-experimental, descriptive study; cost description	n/a	n/a	n/a	Genotyping	n/a	n/a	n/a	Staff time, material costs, overheads	n/s	n/a	Laboratory	$8.62/test
Ropert-Bouchet, 2012 [84]	50%	France	Non-experimental, descriptive study; cost description	People with HH	n/a	n/a	n/a	n/a	n/a	n/a	Blood tests, medical consultations, hospital costs	n/a	n/a	Third party payer	n/a
Categorised low quality (n=12); quality score <50%															
Barton et al, 2002 [75]	44%	US	Quasi-experimental; CEA	Workplace	2,199	n/a	Phenotype	TfS >50% for ♀ and >60% for ♂; SF >200ng/ml for ♂ and >300ng/ml for ♀	n/a	n/a	Blood tests, general and specialist medical consultations, liver biopsy, (paid by insurers)	n/s	n/s	Third party payer	$8,826/HH identified
Adams, 1998 [76]	42%	Canada	Quasi-experimental; CEA	Children of HMZ	291	n/a	Phenotype v. spousal genotyping	TfS<55% for ♀ and >60% for ♂	n/a	n/a	Blood and DNA tests, medical consultations	n/s	n/a	Health service	$58,200 v. $35,600/strategy

Appendix 2B Table 1: Characteristics of the studies

Jacobs et al, 2005 [77]	40%		quasi-experimental; CEA	Hospital inpatients	456	422	No screening guideline v. sequential	TfS>50% and SF>560ng/ml	n/a	n/a	Laboratory costs for blood and DNA tests, liver biopsy and one day hospital stay	4 yrs	n/a	Third party payer	€2380 v. €2600 (per HH diagnosis pre and post guideline implementation)
Stave et al, 1999 [71]	36%	US	Quasi-experimental; cost description	Workplace	1968	n/a	Phenotype	TfS>50% ♀, 60% ♂; SF >290ng/ml ♀, 322ng/ml ♂; liver biopsy	n/a	n/a	Blood tests, medical consultation	Present	n/a	Third party payer	$27850/program
Bhavnani et al, 2000 [78]	35%	UK	Quasi-experimental; CEA	Blood samples from hospital inpatients, outpatients and GP patients	35,069	n/a	Sequential *(phenotype followed by genotype)*	ALT<50µ/l; TfS<60%	n/a	n/a	Blood and DNA tests	Present	n/a	Laboratory	£117/HH identified
Asberg et al, 2001 [42]	32%	Norway	Quasi-experimental; CEA	General population aged ≥20 years	64,717	n/a	Sequential	TfS ≥50% for ♀ and 55% for ♂; SF 110µg/l for ♀ and 200µg/l for ♂	n/a	n/a	Reagent cost of initial screen, second screen costs and medical consultation	n/s	n/s	Third party payer	$390/HH identified
Baer et al, 1995 [79]	29%	US	Quasi-experimental; CEA	Community health centre; males aged ≥30years	3,977	n/a	Phenotype	TfS≥62%; SF≥500µg/l	n/a	n/a	Blood tests, liver biopsy	n/s	n/a	Third party payer	$65,000/HH identified
Adams et al, 2000 [80]	22%	Canada	Quasi-experimental; CEA	Voluntary blood donors	5,211	n/a	Phenotype (x2) v. genotype UIBC; TfS	TfS>45%	n/a	n/a	Blood tests	n/s	n/a	Service provider	UIBC $5,570/HMZ identified
Lederle, 1989 [85]	22%	US	Non-experimental; cost description	n/a	n/a	n/a	Phenotype	n/a	n/a	n/a	Blood tests, liver biopsy	Present	n/a	n/s	$24,804/HH diagnosis
Balan et al, 1994 [81]	15%	US	Quasi-experimental; CEA	Community health centre	12,258	n/a	Phenotype	Serum Iron≥180µg/dl ; ≥62% SIBC; SF≥400µg/l	n/a	n/a	Blood tests, TV, liver biopsy, medical consultation	1990	n/a	Service provider	$5,631-8,447/HH identified
Timms et al, 2002 [72]	5%	UK	Quasi-experimental; cost description	Community-based patients diagnosed with	128	3011	Genotype: PCR/SSP & PCR/RFLP	n/a	n/a	n/a	DNA tests: laboratory based	Present	n/s	Service provider	£1/test; £64/ HH

Appendix 2B Table 1: Characteristics of the studies

Delaveyne et al, 2004* [89]	-	France	Abstract of CEA; model	chondrocal-cinosis Population screening v. family screening	n/a	n/a	SF and TfS with confirmatory genotyping for C282Y.	n/s	n/r	n/r	n/s	1 year	n/a	n/s	€3.6-19.5 million v. €78,000 (per program)

Treatment and other studies (n=5)

		Origin	Study design	Population	Participants *n*	Control *n*	Intervention	Time horizon	Costs included	Disc-ount rate	Costs	Outcome measure	Outcome
Rombout-Sestrienkova et al, 2012 [55]	79%	Netherlands	RCT; cost analysis	Newly diagnosed HH patients	19	19	Treatment: phlebotomy v. erythrocytapheresis	3 years	Treatment and productivity	n/a	Direct and indirect	€/procedure; Total mean costs (€)	€71.49 v. €251.18 (per procedure); €4438 v. €3005
Mariani et al, 2005 [56]	53%	Italy	Non-experimental-descriptive, case series; cost analysis	Patients with severe HH	3	n/a	Treatment: erythrocytapheresis plus erythropoietin v. phlebotomy	n/a	Treatment sessions	n/s	Direct	€/treatment	€602 v. €35 (Total mean costs)
Stefashyna et al, 2014 [57]	38%	Switzerland	Quasi-experimental; cost analysis	Volunteer blood donors	86 donors with early, uncomplicated HH	n/a	whole blood donation v. double-erythrocytapheresis	n/s	Treatment	n/s	Direct	USD/treatment	USD186 v. 238, but fewer treatments required for latter.
Gribble et al, 2009 [59]	38%	US	Non-experimental; cost description	HH blood donors	17	17 (retrospective case review of same cohort)	n/a	1 year	TV, blood donations	n/a	Direct	Net revenue pre and post FDA variance for blood donations	$6000 v. $20345
Dye et al, 2011 [58]	n/a	Australia	Non-experimental, cost analysis	Hospital morbidity data system	n/a	n/a	n/a	6 years	hospitalisations	n/a	Direct	$/patient, $/admission	$21,349, $2,827

Note: * abstract only; ~ refers to prevalence of HH and suspected iron overload in population; # of those interested in screening. ~ Cost saving refers to total cost of caring for a HMZ with no screening minus the total cost of screening, calculated for a range of ages

ASO allele-specific oligonucleotide; C cascade screening; CEA cost effectiveness analysis; CUA cost utility analysis; EAMR refers to Excess annual mortality rate; HH person with hereditary haemochromatosis; HMZ homozygote; LYG Life Year gained; MRI magnetic resonance imaging; n/a not applicable; n/s not stated; P population screening; PCR polymerase chain reaction; RFLP restriction fragment length polymorphism; SF serum ferritin; Sfe serum iron; SIBC saturation of iron binding capacity; SPOLA Solid-phase oligonucleotide ligation assay; SSP sequence specific primers; TfS Transferrin saturation; TIBC Total iron binding capacity; UIBC unsaturated iron binding capacity.

USD = US Dollar, EUR = Euro, GBP = British Pound, AUD = Australian Dollar, CAD = Canadian Dollar

PR refers to prevalence, PE to penetrance, I=interested in screening, U= uptake of screening, A= adherence to treatment

Chapter 3: Quality of life utility values for hereditary haemochromatosis in Australia

3.1 Preface

When considering the introduction of a new health intervention, it is important to establish the clinical, quality of life and economic burdens associated with the targeted condition, i.e. the size of the problem that screening is seeking to prevent, and thus the potential gains to be made. Health state utility is of particular interest as it captures the quality of life burden associated with haemochromatosis disease states, and is a metric that can be used in health economic evaluations.

The preceding chapter presented a summary of the global evidence relating to health economic aspects of hereditary haemochromatosis. Whilst no robust health state utility data for people with haemochromatosis was identified in the review, four studies incorporated utility values in modelled evaluations of the cost-effectiveness of screening for haemochromatosis. These studies used utility values set at unrealistically high levels, of unknown sources. The use of inaccurate utility estimates will likely result in incorrect estimates of the incremental cost-effectiveness associated with an intervention.

Chapter 3 presents the results of a cross-sectional observational study reporting health state utility values for a haemochromatosis cohort. A national, online survey was conducted, which allowed for the calculation of utilities for different categories of severity of haemochromatosis. These utility values, which provide insight into the quality of life impacts related to haemochromatosis, are the first to be published, and can be incorporated into health economic models for haemochromatosis.

This chapter has been published in *Health and Quality of Life Outcomes* (Appendix 3A).

de Graaff, B., Neil, A., Sanderson, K., Yee, K.C. & Palmer AJ. “Quality of life utility values for hereditary haemochromatosis in Australia” *Health and Quality of Life Outcomes*. February 2016; 14(31).

3.2 Abstract

AIM: Hereditary hemochromatosis (HH) is a common autosomal recessive disorder amongst persons of northern European heritage. If untreated, iron accumulates in parenchymal tissues causing morbidity and mortality. As diagnosis often follows irreversible organ damage, screening programs have been suggested to increase early diagnosis. A lack of economic evidence has been cited as a barrier to establishing such a program. Previous analyses used poorly estimated utility values. This study sought to measure utilities directly from people with HH in Australia.

METHODS: Volunteers with HH were recruited to complete a web-based survey. Utility was assessed using the Assessment of Quality of Life 4D (AQOL-4D) instrument. Severity of HH was graded into four categories. Multivariable regression analysis was performed to identify parameters associated with HSUV.

RESULTS: Between November 2013 and November 2014, 221 people completed the survey. Increasing severity of HH was negatively associated with utility. Mean (standard deviation) utilities were 0.76 (0.21), 0.81 (0.18), 0.60 (0.27), and 0.50 (0.27) for categories 1-4 HH respectively. Lower mean utility was found for symptomatic participants (categories 3 and 4) compared with asymptomatic participants (0.583 v. 0.796). Self-reported HH-related symptoms were negatively associated with HSUV (r=-0.685).

CONCLUSIONS: Symptomatic stages of HH and presence of multiple self-reported symptoms were associated with decreasing utility. Previous economic analyses have used higher utilities which likely resulted in underestimates of the cost effectiveness of HH interventions. The utilities reported in this paper are the most robust available, and will contribute to improving the validity of future economic models for HH.

3.3 Introduction

Hereditary hemochromatosis (HH) is a common autosomal recessive disorder in populations of northern European heritage [1, 2]. It is characterised by increased iron absorption caused by a defect in the HFE gene. Several mutations have been identified: C282Y, H63D and S56C [3-5]. C282Y homozygosity accounts for 80 to 90% of people diagnosed with iron-overload, with the other mutations uncommonly associated with iron overload. [6, 7]. It has been hypothesised that HH is most prevalent in northern European populations due to a mutation occurring in Central Europe, hence the description 'Celtic mutation" [8]. Prevalence of C282Y homozygosity has been reported to be between 1 in 150 to 200 persons of Northern European ancestry. Amongst populations of different heritage, prevalence is much lower: 1 in 300 Hispanics; 1 in 1,000 Native Americans; 1 in 1,000, 000 Asians [9-13]. Whilst prevalence of other genotypes is more common (1 in 50 C282Y/H63D compound heterozygotes), the burden of disease associated with these mutations is low [4, 14].

In a proportion of C282Y homozygotes, elevated hepcidin production increases the absorption of dietary iron, which is stored in the parenchymal tissues of the heart, liver and pancreas. If left untreated, iron overload can be a cause of morbidity and mortality, including multiple arthropathies, type 2 diabetes, liver disease and heart disease [15-17]. HH and iron overload is commonly diagnosed by conducting iron studies (transferrin saturation and serum ferritin) with confirmatory genotyping. Treatment consist of regular therapeutic venepuncture.

Rates of clinical penetrance (i.e. expression of disease) reported in literature vary, in part due to different definitions. Some authors have defined penetrance as irreversible organ damage, such as cirrhosis or hepatocellular carcinoma, whilst other have included a spectrum of health states, from elevated iron stores and serum iron through to irreversible organ damage. Recent studies have reported rates of cirrhosis of the liver amongst C282Y homozygotes to be between 2 and 6% [10, 18, 19]. When penetrance is defined as elevated iron stores and serum iron through to irreversible organ damage, rates of 28.4% for male and 1.2% for female C282Y homozygotes have been recently reported [10].

Whilst diagnosis and prevention of iron overload in genetically susceptible patients is

relatively straightforward, the vague nature of early symptomatology, in that this can be experienced by people with clinically normal iron levels, contributes to some patients being diagnosed only after irreversible organ damage has occurred [20-23]. Effective treatment is readily available, therefore early diagnosis and timely treatment leads to substantial improvements in patient outcomes. Population screening strategies have been proposed as an approach to increase early identification of people with HH, thereby reducing the potential burden of disease associated with iron overload [24-28].

Whilst HH is a condition that fulfils several of the criteria set out by the World Health Organisation for population screening programs [29], a lack of robust health economic data has been cited as a hurdle to implementing such a program [24, 25, 30, 31]. Considerable limitations have been identified in the economic evaluations of HH screening programs that have been published to date [32, 33].

Cost effectiveness and cost utility analyses give rise to a ratio of the difference in costs and effectiveness between two or more health interventions. Multi-attribute utility instruments, such as the AQOL-4D and EQ-5D, allow for calculation of an individual's utility. Quality adjusted life years (QALYs) are calculated by combining a utility with an outcome such as life years gained (LYG). QALYs are the preferred unit of measurement of many decision makers, such as the UK's National Institute for Health and Care Excellence (NICE) [34] and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) [35].

Cost effectiveness analyses and cost utility analyses give rise to a ratio of the difference in costs and effectiveness between two or more health interventions. The cost of an intervention is measured in monetary units and effectiveness may be measured unidimensionally for cost effectiveness analyses (e.g. life years gained) or by means of a multidimensional instrument (such as the EQ-5D, SF-6, AQOL-4D) for cost utility analyses. Importantly, multi-attribute utility instruments allow for calculation of an individual's utility (HSUV): a measure of the strength of preference for a particular health state. Utilities are measured on a scale of zero to one, with one representing full health, and zero, death. Some instruments such as the AQOL-4D and the EQ-5D allow for negative values, as certain states may be considered worse than death [36, 37]. When a utility is combined with life years gained (LYG), the outcome reflects both morbidity and mortality: quality adjusted life years

(QALYs). A cost per QALY can then be reported, the preferred unit of measurement of many decision makers, such as the UK's National Institute for Health and Care Excellence (NICE) [34] and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) [35].

To date, just four cost utility studies of HH screening programs have been published [33]. The studies did not report the sources of the utilities used, and the estimates employed for conditions such as healthy state, heart disease and cirrhosis of the liver were markedly higher than reported for comparable populations [33]. Such use of elevated utility values is likely to result in underestimates of the potential gains associated with screening programs, which in turn may impact on policy decisions regarding provision of HH screening programs.

The purpose of this study was to assess the utilities for a sample of people with HH with different stages of disease severity using a multi-attribute utility instrument.

3.4 Methods

A web-based cross-sectional study using convenience sampling was conducted across Australia. Multiple recruitment strategies were used: the national support group, Hemochromatosis Australia (HA), sent emails to all members on behalf of the researchers informing them of the project and the web address; the link to the survey was placed on HA's website; flyers outlining the study were sent to large Australian metropolitan hepatology, haematology and gastroenterology clinics, along with general practitioners sourced from HA's referral network; advertisements were placed on social media sites; and newspaper articles about the condition and the study were published. In addition, case finding was conducted in all Tasmanian public hospitals. All patients admitted between July 2009 and June 2014 with a diagnosis of HH, as identified in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) by code E831: Disorders of Iron Metabolism, were sent letters by the research group, informing them of the study and inviting them to participate. Only names and postal details were supplied to the researchers. Eligibility criteria included a diagnosis of haemochromatosis, residing in Australia, aged 18 or older and provision of written informed consent. The survey instrument is included in Appendix 3B. Ethical approval for the study was granted by the Tasmanian Health and Medical Research Ethics Committee (H0013564).

Measurements

HSUV

Utility was measured using the Assessment of Quality of Life 4D instrument (AQOL-4D) [38]. The AQOL-4D is a 12 item questionnaire that provides a global health state utility value. It consists of four separate dimensions: independent living, relationships, mental health and senses. The HSUV is scored on a scale from -0.04 to 1.00. A score of one represents optimal health, a score of zero represents a state equivalent to death, and scores less than zero represent states worse than death [38]. This instrument was chosen as it is sensitive to a broad range of conditions and health states [39], Australian population normative data were available for comparison [40], and due to cost and software limitations associated with the use of other instruments. AQOL HSUV were calculated using syntax supplied by the AQOL Group [41].

HH-related health states

Stages of HH were categorised using the framework published by the European Association for the Study of the Liver (EASL) [16]. The expert panel identified a lack of generalizability of much of the research into HH, in part due to researchers and clinicians using different definitions or descriptions of HH, i.e. genetic mutation only, through to organ damage. To address this, EASL recommended using uniform categorisation of the different stages of HH. These categories are described in Table 1. Participants were provided with this matrix, and asked to categorise their condition. These self-categorisations were verified by cross-checking responses with regard to recent experience of HH comorbidities. Just one discrepancy was identified: recoding for the more conservative categorisation was carried out and comorbidities were assumed to be unrelated to HH.

Table 1: Categories of HH [11]

Category 1	Genetic mutation only (C282Y homozygotes, H63D heterozygotes and compound heterozygotes)
Category 2	Genetic mutation and elevated iron studies, either transferrin saturation or serum iron
Category 3	Genetic mutation, elevated iron levels and early symptoms, including arthritis, fatigue
Category 4	Genetic mutation, elevated iron levels and organ damage

Lists of commonly reported HH-related comorbidities and symptoms were compiled following a review of the literature. Comorbidities included osteoarthritis, liver diseases (fibrosis, cirrhosis, hepatocellular carcinoma), heart failure, cardiomyopathy, Type 2 diabetes and porphyria cutanea tarda. Participants were asked if they had been diagnosed with each condition and if it was a) related to HH, b) not related to HH, or c) unsure if related to HH. Only conditions for which the participant stated were related to HH were included in analyses. In order to capture data on possible undiagnosed comorbidities and general symptoms of iron overload, participants were asked if they had experienced a range of symptoms in the last three months that they considered were related to HH. Symptoms associated with HH included the general effects of iron overload, such as fatigue, along with symptoms of liver disease, heart failure, cardiomyopathy, arthritis, porphyria cutanea tarda and changes to the reproductive system (e.g. decreased libido).

Statistical analyses

Statistical analyses were performed using SPSS version 20.0.0. Chi square and ANOVA were used for descriptive statistics. Differences between HH utilities and data from other population groups were analysed using T-tests and Kruskal Wallis one way analysis of variance. Linear regression was carried out to identify the association between co-morbidity count and utility. Pearson correlation coefficients were calculated for utility values and severity of HH.

3.5 Results

Demographics

Two hundred and seventy participants self-completed a web-based survey between November 2013 and November 2014 as part of a national cost of illness study for HH. Two hundred and twenty one participants completed the AQOL-4D. The demographic characteristics of participants are presented in Table 2. The only notable difference between participants who completed the AQOL-4D and those who did not was that the former were more likely to be employed full time (X^2=4.254, p=0.026) (Table 2).

Due to the sampling techniques, it is not possible to quantify the number of people who

viewed information regarding the study, thus calculating a response rate. However, for the case finding at all Tasmanian public hospitals, a response rate of 20% was observed (37 participants from 189 letters).

Table 2: Demographic characteristics of the sample

	AQol-4D completers n=221	AQoL-4D non-completers n=47	p value
Age, mean ±SD	52.7 ±14.2	53.6±13.2	0.694
Sex (male)	41.6%	41.3%	0.552
Relationship status:			
currently married/defacto	79.6%	68.1%	0.066
Country of birth:			
Australia	83.7%	85.1%	0.506
United Kingdom	9.0%	8.5%	0.584
Highest level of education completed*:			
<yr 12	24.7%	25.0%	0.565
certificate, Trade etc	31.7%	39.4%	0.245
yr 12	10.4%	3.0%	0.149
uni +	35.7%	33.3%	0.476
Labour force participation:			
employed full time	32.1%	17.0%	0.026
employed part-time	15.4%	14.9%	0.568
self-employed	9.0%	10.6%	0.455
retired	25.3%	19.1%	0.242
Unemployed	5.4%	4.3%	0.542

* For this question, n=33 for the non-completer group.

AQOL-4D HSUV

The mean utility for all participants using the AQol-4D was 0.66 (±0.26), with a range of -0.04 to 1.00 (95%CI 0.63-0.70) (Table 3). This was lower than the Australian population norm estimated using the AQoL-4D of 0.81 (n=8839, SD=0.22, 95%CI 0.81-0.82) [40].

Univariate analyses were carried out to examine utilities for age and sex (Table 3). This showed similar values for males (0.69) and females (0.64) (p=0.163). Utilities were also

examined by age deciles and sex. Whilst slightly higher mean utility values were reported for males for most age deciles, none of these differences were found to be statistically significant. Overall, utility was highest for participants aged between 30 and 39 (0.72), and lowest for those aged 70-79 (0.61).

Table 3: Comparison of HH cohort and Australian population normative utility values [23]

Variables	Mean HSUV	95% CI	n	Males			Females			Population norm HSUV	95% CI
				Mean HSUV	95% CI	n	Mean HSUV	95% CI	n		
Age group:											
20-29	0.67	0.55-0.80	10	0.75	0.53-1.00	2	0.65	0.49-0.70	8	0.86	0.85-0.87
30-39	0.72	0.62-0.80	30	0.78	0.66-0.90	7	0.70	0.59-0.81	23	0.84	0.83-0.85
40-49	0.66	0.57-0.74	39	0.72	0.57-0.84	15	0.62	0.50-0.74	24	0.81	0.80-0.82
50-59	0.63	0.54-0.70	52	0.62	0.47-0.75	19	0.63	0.54-0.71	33	0.80	0.78-0.81
60-69	0.67	0.61-0.73	67	0.70	0.62-0.78	34	0.65	0.54-0.74	33	0.80	0.78-0.81
70-79	0.61	0.47-0.73	16	0.63	0.47-0.76	11	0.56	0.21-0.92	5	0.76	0.76-0.79
Sex											
Male	0.69	0.64-0.75	92							0.82	0.81-0.83
Female	0.64	0.60-0.69	129							0.81	0.80-0.81
All	0.66	0.63-0.70	221							0.81	0.81-0.82

Note: HSUV refers to health state utility values; 95%CI refers to the 95% confidence interval

Reporting of utility by stages of severity of HH (Table 1) can help mitigate any bias due to the sampling approach. A trend of decreasing HSUV was identified with stages three and four (Table 4). A Pearson correlation coefficient was calculated to assess the relationship between mean utility and stages of HH: a moderate negative correlation was found (r= -0.366; p<0.001). Whilst lower mean HSUV were reported for female participants for each category, these differences were not significant.

Table 4: Mean utility values by categories of HH by sex

Categories of HH	HSUV mean	SD	n	95%CI
All participants				
Category 1	0.76	0.21	20	0.67-0.85
Category 2	0.81	0.18	63	0.76-0.85
Category 3	0.60	0.27	115	0.55-0.658
Category 4	0.50	0.27	23	0.39-0.61
All categories	*0.66*	*0.26*	*221*	*0.63-0.70*
Males				
Category 1	0.88	0.10	6	0.78-0.98
Category 2	0.85	0.12	29	0.80-0.89
Category 3	0.59	0.28	45	0.51-0.68
Category 4	0.59	0.23	12	0.44-0.74
All categories	*0.69*	*0.27*	*92*	*0.64-0.75*
Females				
Category 1	0.71	0.235	14	0.58-0.84
Category 2	0.77	0.21	34	0.70-0.85
Category 3	0.60	0.26	70	0.54-0.66
Category 4	0.41	0.29	11	0.22-0.60
All categories	*0.64*	*0.26*	*129*	*0.60-0.69*

Note: HSUV refers to health state utility values; SD standard deviation; 95%CI refers to the 95% confidence interval

To investigate the impact of symptomatic HH on utility, the four categories of HH were combined into asymptomatic (categories 1 and 2), and symptomatic (categories 3 and 4) participants. Utility was significantly lower for the symptomatic group for males (0.85 v. 0.59: H=25.36, p<0.001), females (0.75 v. 0.58: H=14.90, p<0.001) and overall (0.80 v. 0.58: H=38.79, p<0.001) (Table 5).

Table 5: Mean utility values of symptomatic HH

Categories of HH	HSUV mean	SD	n	95%CI	Between groups*
All participants					
Categories 1 & 2	0.80	0.19	83	0.76-0.84	H=38.79, p<0.001
Categories 3 & 4	0.58	0.27	138	0.54-0.63	
All categories	*0.66*	*0.26*	*221*	*0.63-0.70*	
Males					
Categories 1 & 2	0.85	0.11	35	0.82-0.89	H=25.36, p<0.001
Categories 3 & 4	0.59	0.27	57	0.52-0.67	
All categories	0.69	0.26	92	0.64-0.75	
Females					
Categories 1 &2	0.75	0.22	48	0.69-0.82	
Categories 3 & 4	0.58	0.27	81	0.52-0.64	H=14.90, p<0.001
All categories	0.64	0.64	129	0.60-0.69	

Note: HSUV refers to health state utility values; SD standard deviation; 95%CI refers to the 95% confidence interval
* Kruskal Wallis one way analysis of variance was used for this test for significance.

In keeping with these findings, evaluation of the impact of HH related comorbidities on utility found all comorbidities were related to lower mean utility than reported for participants reporting no comorbidities (0.76) and the entire HH cohort (0.66) (Table 6). Using the sample mean utility value as the reference case (0.66), participants self-reporting arthritis related to HH had a lower mean utility (0.52: $F(1,198)=10.854$, $p=0.001$). Whilst lower mean utility values were reported for fibrosis, cirrhosis, heart failure, cardiomyopathy, diabetes and porphyria cutanea tarda, only small numbers of participants reported these co-morbidities, therefore these should be interpreted with caution (Table 6).

Participants were also asked to report on experience of symptoms related to HH and iron overload in the preceding three months (Table 7). Participants were asked if they thought these symptoms were related to HH, possibly related or not related. Only participants reporting their symptoms to be related to HH were included to minimise over-reporting. Of a maximum of 20 symptoms and conditions, the median number experienced by the sample was 3 (SD=3.8, range 0-15). When compared with the reference HSUV, all symptoms were associated with lower utility. A Pearson correlation coefficient was calculated to assess the relationship between symptom count and HSUV, and a strong negative correlation was found ($r= -0.685$; $p<0.001$) (Figure 1).

Table 6: Mean utility values by self-reported HH-related comorbidities

HH-related comorbidities*	mean HSUV	SD	n
All participants			
no comorbidity	0.76	0.21	100
arthritis	0.52	0.25	35
fibrosis	0.53	0.29	7
cirrhosis	0.61	0.31	5
heart failure	0.58	0.24	3
cardiomyopathy	0.30	-	1
diabetes	0.52	0.33	4
porphyria cutanea tarda	0.02	-	1
Males			
no comorbidity	0.76	0.25	39
arthritis	0.59	0.23	15
fibrosis	0.69	0.05	5
cirrhosis	0.74	0.16	3
Females			
no comorbidity	0.76	0.19	61
arthritis	0.48	0.26	20
fibrosis	0.12	0.02	2
cirrhosis	0.42	0.45	2

Note: HSUV refers to health state utility values; SD standard deviation

*Participants were asked if they had been diagnosed with these conditions and that they were considered to be related to HH and iron overload. Participants with these conditions, but were unsure if they were related to HH were not included in this analysis.

Figure 1: Linear regression of HSUV and symptom count related to HH

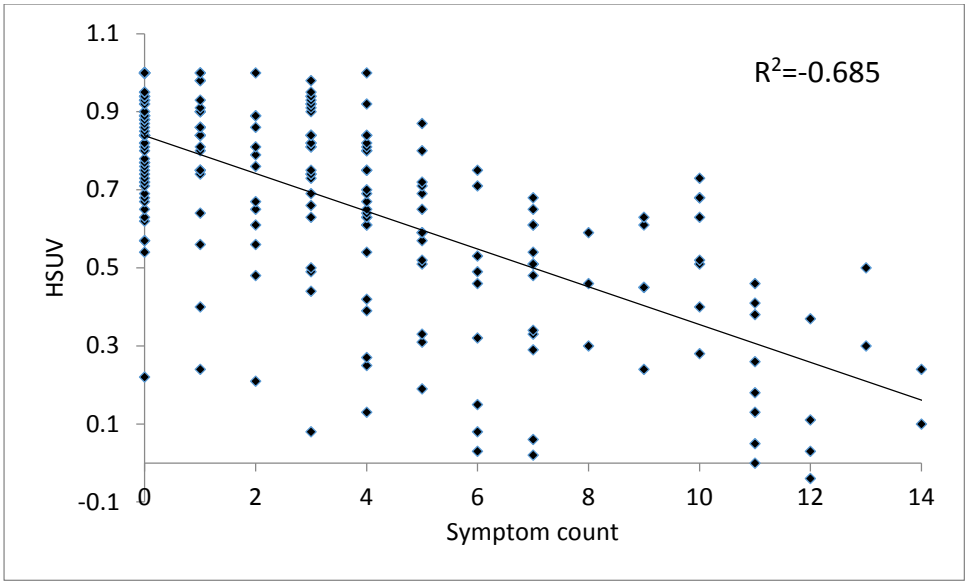

Table 7: Mean utility values for HH related symptoms

Experienced in the last 3 months	mean HSUV	SD	n	Males			Females		
				mean HSUV	SD	n	mean HSUV	SD	n
General effects									
Chronic fatigue	0.55	0.29	102	0.56	0.306	37	0.55	0.29	65
Weakness	0.49	0.26	87	0.51	0.28	33	0.48	0.26	54
Unexplained weight loss	0.42	0.40	10	1.00	-	1	0.35	0.36	9
Unexplained weight gain	0.50	0.26	30	0.37	0.31	8	0.55	0.23	22
Liver disease									
Abdominal swelling	0.40	0.25	35	0.41	0.33	9	0.39	0.22	26
Abdominal pain/discomfort	0.47	0.26	47	0.51	0.31	12	0.46	0.25	35
Enlarged liver (hepatomegaly)	0.40	0.24	15	0.57	0.19	6	0.29	0.21	9
Heart-related problems									
Swelling of your feet and/or ankles	0.46	0.23	47	0.43	0.24	17	0.48	0.22	30
Shortness of breath-walking quickly or uphill	0.50	0.27	64	0.54	0.27	24	0.48	0.26	40
Shortness of breath-walking on level ground	0.36	0.26	29	0.39	0.26	14	0.33	0.27	15
Shortness of breath-resting in a chair	0.31	0.25	8	0.32	0.45	3	0.21	0.24	5
Heart failure or weak heart	0.30	-	1	0.30	-	1	-	-	-
Abnormal heart rhythm/ arrhythmia	0.55	0.23	25	0.61	0.17	8	0.52	0.26	17
Heart disease	0.52	0.27	6	0.49	0.28	5	0.71	-	1
Arthritis									
Swollen/tender metacarpophalangeal joints (fingers/hands)	0.48	0.25	58	0.47	0.30	21	0.49	0.22	37
Other joint stiffness/pain/ache	0.55	0.26	96	0.6	0.26	39	0.51	0.24	57
Skin changes									
Change in skin colour	0.45	0.29	25	0.50	0.35	8	0.43	0.27	17
Increased facial hair growth	0.32	0.21	14	-	-	-	0.32	0.21	14
Reproductive									
Loss of libido and/or erectile dysfunction	0.49	0.27	49	0.48	0.27	17	0.49	0.28	32
Unexplained confusion and/or memory loss	0.40	0.24	53	0.39	0.25	18	0.41	0.24	35

Note: HSUV refers to health state utility values; SD standard deviation

3.6 Discussion

This is the first study that reports HSUV measured directly from a cohort with HH. This is of importance, as a lack of robust health economic data has been cited as a barrier to implementing population screening programs for HH [25, 30, 31, 42]. The utility values calculated in this study provide robust estimates that can be used in future economic models of screening interventions. Whilst the sampling strategy may have introduced bias, this has been mitigated by reporting utility values for categories of HH rather than across the study population in general. These values can then be used in combination with penetrance rates in economic models for HH interventions.

Symptomatic stages of HH (categories three and four [25]) were associated with lower utility than asymptomatic stages. The values for all four categories are useful, as they incorporate all aspects of HH and related conditions and can be used to populate cost utility analyses (CUA) health economic models. Previous CUA models have only incorporated specific comorbidities which are associated with significant morbidity and mortality: cirrhosis, diabetes and heart failure, with no consideration of common comorbidities such as arthritis, or symptoms such as fatigue. This may be related to the relatively high prevalence of both fatigue and arthritis amongst other populations, and the difficulties surrounding the aetiologies of both, however there is evidence suggesting that the prevalence of both is higher amongst some HH patients. The prevalence of fatigue amongst general practice patients has been estimated to be between 1.4-7.0% of encounters [43-46]. Work by Allen and colleagues has reported a much higher rate of 22% for C282Y homozygotes with elevated serum ferritin levels (greater than 1,000µg/l) [10]. Similarly, arthritis, specifically osteoarthritis, is prevalent in Australia, with 9% reporting this condition [47]. Allen and colleagues reported use of arthritis medication as a proxy measure for arthritis, noting that 20% of C282Y homozygotes with serum ferritin greater than 1,000µg/l reported use of these medications. In combination, these data guided the decision to include arthritis and fatigue in the current study.

To date, just four CUA have been published on HH screening programs, none of which cited the sources of the utility values employed [7, 48-50]. Values were assigned for cirrhosis, diabetes and heart failure, and in some cases, combinations of these. In a Norwegian study

[48], a basal utility value of 1.00 was assumed for all HH conditions except cirrhosis, which was assigned a utility of 0.95, values that are substantially higher than those reported here. Two Canadian studies, by the same research group, used utilities of 0.8 for cirrhosis, 0.9 for diabetes, 0.5 for heart failure, 0.72 for cirrhosis and diabetes, 0.78 for cirrhosis and heart failure, 0.87 for diabetes and heart failure and 0.70 for a combination of cirrhosis, diabetes and heart failure [7, 49]. A fourth study did not provide the utility values used in the modelling [50]. Some concerns arise in respect of these estimates. First, in comparing these utility values to US population normative data, a disparity appears: the mean utility derived from the SF-6D ranged from 0.79 to 0.81 for persons aged 35 to 74, and similarly, using the EQ-5D, mean utility ranged between 0.87 and 0.89 [51]. The fact that the utility estimates that were used in cost utility analyses for participants with health conditions such as cirrhosis and diabetes are similar to or higher than those reported for the general US population indicates these estimates may be incorrect. The likely overestimates of HSUV for HH-related conditions are likely to lead to underestimates of potential utility gains associated with screening interventions.

Second, disease specific HSUV used in these cost utility analyses are also higher than suggested in published literature. A meta-analysis of utility values for liver diseases using a range of approaches to measure utility reported a mean of 0.75 for compensated cirrhosis (range 0.65-0.90) and 0.67 for decompensated cirrhosis (range 0.57-0.81) [52]. Whilst our study did not differentiate cirrhosis in this manner, amongst the small number of participants reporting this condition (n=5), the mean utility (0.61) was slightly lower than reported for decompensated cirrhosis but within the range reported. In contrast, the published cost utility analyses used values of 0.95 [48] and 0.8 [7, 49], higher than the mean values reported for both compensated and decompensated cirrhosis [52]. Similarly, a meta-analysis of utility values for diabetes reported a mean of 0.76 (range 0.53-0.88) [53]. In our study, a mean of 0.52 was reported (n=4), slightly lower than the lower range reported in this meta-analysis. In the three HH CUA, one used a utility value for diabetes of 1.00 [48], and two used a value of 0.9 [7, 49], both notably higher than published estimates.

Mean utility for heart failure varies depending on the severity of the condition. From a large, multi-site trial that used the EQ-5D, mean utility for different levels of severity based on the New York Heart Association (NYHA) classifications were: class I: 0.815, class II: 0.720, class III: 0.590, class IV: 0.508 [54]. Our study reported a mean of 0.58, however data were available for only three participants, and all were in different NYHA classes. The two Canadian CUA models used a utility value of 0.5 [7, 49], which is similar to the NYHA class 4. In contrast, the Norwegian study assumed a utility of 1.00, which is not in keeping with estimates in the current literature [48].

To date, no HH CUA has incorporated HSUV related to arthritis. This is surprising as arthritis related to iron overload is commonly reported amongst patients diagnosed with HH [10, 55-57]. Whilst HRQoL is not synonymous with HSUV, it can serve as an indicator. A study examining the effects of a range of HH-related comorbidities using the SF-36 found that, compared to cirrhosis and diabetes, arthritis was the single strongest factor that impacted on HRQoL [58]. Whilst the paper was published in 1996, no subsequent studies have incorporated utility values for arthritis. Hawthorne and colleagues, using the AQOL-4D, reported the Australian normative utility value for arthritis as 0.69 (SD 0.26). Our study reported a lower mean value of 0.52 (SD 0.25, n=35). In the current study, both self-reported diagnosis of arthritis related to HH and symptoms suggestive of arthritis were associated with lower mean utility than the sample mean (0.52, 0.48, 0.66 respectively).

Limitations of this study include cross-sectional design and use of convenience sampling. Convenience sampling, which was used as a result of available resourcing, may limit the generalizability of these results. Further, the majority of the respondents were female, despite higher penetrance amongst males. To minimise sampling bias, we have focused on utility values for categories of disease and symptomatology for males and females separately. Whilst an overall sample mean HSUV is likely to be affected by under- or over-reporting from participants with more health problems, the mean values for each category are not affected. This allows for these values, in combination with penetrance estimates from robust epidemiological studies, to be used in HH health economic models.

A further limitation of this study was the reliance on participants' self-report regarding experience of HH related comorbidities and symptoms. Whilst participants were asked if the comorbidities were related to HH, even with clinical verification, it is difficult to be certain of the aetiology of these. Whilst it can be argued that there may be some over-reporting of symptoms and comorbidities believed to be caused by HH, to minimise this possibility, cases in which participants were unsure of the aetiology have been excluded. Symptoms and comorbidities were only included when participants stated that they were related to HH. Lastly, the small number of participants reporting HH-related comorbidities was also a limitation. Whilst utility values were calculated wherever possible, the small number of respondents means that these data should be interpreted with caution and that no meaningful comparisons can be made between these comorbidities.

In conclusion, this is the first study to report utility values measured directly from people with HH. Despite study limitations, these values are the best available to date, and can be used to populate health economic models investigating the cost utility of HH interventions.

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Quality of life utility values for hereditary haemochromatosis in Australia

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Abstract

Background: Hereditary hemochromatosis (HH) is a common autosomal recessive disorder amongst persons of northern European heritage. If untreated, iron accumulates in parenchymal tissues causing morbidity and mortality. As diagnosis often follows irreversible organ damage, screening programs have been suggested to increase early diagnosis. A lack of economic evidence has been cited as a barrier to establishing such a program. Previous analyses used poorly estimated utility values. This study sought to measure utilities directly from people with HH in Australia.

Methods: Volunteers with HH were recruited to complete a web-based survey. Utility was assessed using the Assessment of Quality of Life 4D (AQOL-4D) instrument. Severity of HH was graded into four categories. Multivariable regression analysis was performed to identify parameters associated with HSUV.

Results: Between November 2013 and November 2014, 221 people completed the survey. Increasing severity of HH was negatively associated with utility. Mean (standard deviation) utilities were 0.76 (0.21), 0.81 (0.18), 0.60 (0.27), and 0.50 (0.27) for categories 1–4 HH respectively. Lower mean utility was found for symptomatic participants (categories 3 and 4) compared with asymptomatic participants (0.583 v. 0.796). Self-reported HH-related symptoms were negatively associated with HSUV ($r = -0.685$).

Conclusions: Symptomatic stages of HH and presence of multiple self-reported symptoms were associated with decreasing utility. Previous economic analyses have used higher utilities which likely resulted in underestimates of the cost effectiveness of HH interventions. The utilities reported in this paper are the most robust available, and will contribute to improving the validity of future economic models for HH.

Background

Hereditary hemochromatosis (HH) is a common autosomal recessive disorder in populations of northern European heritage [1, 2]. It is characterised by increased iron absorption caused by a defect in the HFE gene. Several mutations have been identified: C282Y, H63D and S56C [3–5]. C282Y homozygosity accounts for 80 to 90 % of people diagnosed with iron-overload, with the other mutations uncommonly associated with iron overload [6, 7]. It has been hypothesised that HH is most prevalent in northern European populations due to a mutation occurring in Central Europe, hence the description 'Celtic mutation" [8]. Prevalence of C282Y homozygosity has been reported to be between 1 in 150 to 200 persons of Northern European ancestry. Amongst populations of different heritage, prevalence is much lower: 1 in 300 Hispanics; 1 in 1,000 Native Americans; 1 in 1,000, 000 Asians [9–13]. Whilst prevalence of other genotypes is more common (1 in 50 C282Y/H63D compound heterozygotes), the burden of disease associated with these mutations is low [4, 14].

In a proportion of C282Y homozygotes, elevated hepcidin production increases the absorption of dietary iron, which is stored in the parenchymal tissues of the heart, liver and pancreas. If left untreated, iron overload can be a cause of morbidity and mortality, including multiple arthropathies, type 2 diabetes, liver disease and heart disease [15–17]. HH and iron overload is commonly diagnosed by conducting iron studies (transferrin saturation and serum ferritin) with confirmatory genotyping. Treatment consists of regular therapeutic venesection.

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Rates of clinical penetrance (i.e. expression of disease) reported in the literature vary, in part due to different definitions. Some authors have defined penetrance as irreversible organ damage, such as cirrhosis or hepatocellular carcinoma, whilst other have included a spectrum of health states, from elevated iron stores and serum iron through to irreversible organ damage. Recent studies have reported rates of cirrhosis of the liver amongst C282Y homozygotes to be between 2 and 6 % [10, 18, 19]. When penetrance is defined as elevated iron stores and serum iron through to irreversible organ damage, rates of 28.4 % for male and 1.2 % for female C282Y homozygotes have been recently reported [10].

Whilst diagnosis and prevention of iron overload in genetically susceptible patients is relatively straightforward, the non-specific nature of early symptomatology, in that this can be experienced by people with clinically normal iron levels, contributes to some patients being diagnosed only after irreversible organ damage has occurred [20–23]. Effective treatment is readily available, therefore early diagnosis and timely treatment leads to substantial improvements in patient outcomes. Population screening strategies have been proposed as an approach to increase early identification of people with HH, thereby reducing the potential burden of disease associated with iron overload [24–28].

Whilst HH is a condition that fulfils several of the criteria set out by the World Health Organisation for population screening programs [29], a lack of robust health economic data has been cited as a hurdle to implementing such a program [24, 25, 30, 31]. Considerable limitations have been identified in the economic evaluations of HH screening programs that have been published to date [32, 33].

Cost effectiveness analyses and cost utility analyses give rise to a ratio of the difference in costs and effectiveness between two or more health interventions. The cost of an intervention is measured in monetary units and effectiveness may be measured unidimensionally for cost effectiveness analyses (e.g. life years gained) or by means of a multidimensional instrument (such as the EQ-5D, SF-6, AQOL-4D) for cost utility analyses. Importantly, multi-attribute utility instruments allow for calculation of an individual's utility (HSUV): a measure of the strength of preference for a particular health state. Utilities are measured on a scale of zero to one, with one representing full health, and zero, death. Some instruments such as the AQOL-4D and the EQ-5D allow for negative values, as certain states may be considered worse than death [36, 37]. When a utility is combined with life years gained (LYG), the outcome reflects both morbidity and mortality: quality adjusted life years (QALYs). A cost per QALY can then be reported, the preferred unit of measurement of many decision makers, such as the UK's National Institute for Health and Care Excellence (NICE) [34] and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) [35].

To date, just four cost utility studies of HH screening programs have been published [33]. The studies did not report the sources of the utilities used, and the estimates employed for conditions such as healthy state, heart disease and cirrhosis of the liver were markedly higher than reported for comparable populations [33]. Such use of elevated utility values is likely to result in underestimates of the potential gains associated with screening programs, which in turn may impact on policy decisions regarding provision of HH screening programs.

The purpose of this study was to assess the utilities for a sample of people with HH with different stages of disease severity using a multi-attribute utility instrument.

Methods

A web-based cross-sectional study using convenience sampling was conducted across Australia. Multiple recruitment strategies were used: the national support group, Hemochromatosis Australia (HA), sent emails to all members on behalf of the researchers informing them of the project and the web address; the link to the survey was placed on HA's website; flyers outlining the study were sent to large Australian metropolitan hepatology, haematology and gastroenterology clinics, along with general practitioners sourced from HA's referral network; advertisements were placed on social media sites; and newspaper articles about the condition and the study were published. In addition, case finding was conducted in all Tasmanian public hospitals. All patients admitted between July 2009 and June 2014 with a diagnosis of HH, as identified in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) by code E831: Disorders of Iron Metabolism, were sent letters by the research group, informing them of the study and inviting them to participate. Only names and postal details were supplied to the researchers. Eligibility criteria included a diagnosis of haemochromatosis, residing in Australia, aged 18 or older and provision of written informed consent. Ethical approval for the study was granted by the Tasmanian Health and Medical Research Ethics Committee (H0013564).

Measurements

HSUV

Utility was measured using the Assessment of Quality of Life 4D instrument (AQOL-4D) [38]. The AQOL-4D is a 12 item questionnaire that provides a global health state utility value. It consists of four separate dimensions: independent living, relationships, mental health and senses. The HSUV is scored on a scale from −0.04 to 1.00. A

score of one represents optimal health, a score of zero represents a state equivalent to death, and scores less than zero represent states worse than death [38]. This instrument was chosen as it is sensitive to a broad range of conditions and health states [39], Australian population normative data were available for comparison [40], and due to cost and software limitations associated with the use of other instruments. AQOL HSUV were calculated using syntax supplied by the AQOL Group [41].

HH-related health states

Stages of HH were categorised using the framework published by the European Association for the Study of the Liver (EASL) [16]. The expert panel identified a lack of generalizability of much of the research into HH, in part due to researchers and clinicians using different definitions or descriptions of HH, i.e. genetic mutation only, through to organ damage. To address this, EASL recommended using uniform categorisation of the different stages of HH. These categories are described in Table 1. Participants were provided with this matrix, and asked to categorise their condition. These self-categorisations were verified by cross-checking responses with regard to recent experience of HH comorbidities. Just one discrepancy was identified: recoding for the more conservative categorisation was carried out and comorbidities were assumed to be unrelated to HH.

Lists of commonly reported HH-related comorbidities and symptoms were compiled following a review of the literature. Comorbidities included osteoarthritis, liver diseases (fibrosis, cirrhosis, hepatocellular carcinoma), heart failure, cardiomyopathy, Type 2 diabetes and porphyria cutanea tarda. Participants were asked if they had been diagnosed with each condition and if it was a) related to HH, b) not related to HH, or c) unsure if related to HH. Only conditions for which the participant stated were related to HH were included in analyses. In order to capture data on possible undiagnosed comorbidities and general symptoms of iron overload, participants were asked if they had experienced a range of symptoms in the last three months that they considered were related to HH. Symptoms associated with HH included the general effects of iron overload, such as fatigue, along with symptoms of liver disease, heart failure, cardiomyopathy, arthritis, porphyria cutanea tarda and changes to the reproductive system (e.g. decreased libido).

Table 1 Categories of HH [11]

Category 1	Genetic mutation only (C282Y homozygotes, H63D heterozygotes and compound heterozygotes)
Category 2	Genetic mutation and elevated iron studies, either transferrin saturation or serum iron
Category 3	Genetic mutation, elevated iron levels and early symptoms, including arthritis, fatigue
Category 4	Genetic mutation, elevated iron levels and organ damage

Statistical analyses

Statistical analyses were performed using SPSS version 20.0.0. Chi square and ANOVA were used for descriptive statistics. Differences between HH utilities and data from other population groups were analysed using T-tests and Kruskal Wallis one way analysis of variance. Linear regression was carried out to identify the association between co-morbidity count and utility. A Pearson correlation coefficient was calculated for utility values and severity of HH.

Results

Demographics

Two hundred and seventy participants self-completed a web-based survey between November 2013 and November 2014 as part of a national cost of illness study for HH. Two hundred and twenty one participants completed the AQOL-4D. The demographic characteristics of participants are presented in Table 2. The only notable difference between participants who completed the AQOL-4D and those who did not was that the former were more likely to be employed full time ($X^2 = 4.254$, $p = 0.026$) (Table 2).

Due to the sampling techniques, it is not possible to quantify the number of people who viewed information regarding the study, thus calculating a response rate. However, for the case finding at all Tasmanian public hospitals, a response rate of 20 % was observed (37 participants from 189 letters).

AQOL-4D HSUV

The mean utility for all participants using the AQol-4D was 0.66 (±0.26), with a range of −0.04 to 1.00 (95 % CI 0.63–0.70) (Table 3). This was lower than the Australian population norm estimated using the AQoL-4D of 0.81 ($n = 8839$, SD = 0.22, 95 % CI 0.81–0.82) [40].

Univariate analyses were carried out to examine utilities for age and sex (Table 3). This showed similar values for males (0.69) and females (0.64) ($p = 0.163$). Utilities were also examined by age deciles and sex. Whilst slightly higher mean utility values were reported for males for most age deciles, none of these differences were found to be statistically significant. Overall, utility was highest for participants aged between 30 and 39 (0.72), and lowest for those aged 70–79 (0.61).

Reporting of utility by stages of severity of HH (Table 1) can help mitigate any bias due to the sampling approach. A trend of decreasing HSUV was identified with stages three and four (Table 4). A Pearson correlation coefficient was calculated to assess the relationship between mean utility and stages of HH: a moderate negative correlation was found ($r = -0.366$; $p < 0.001$). Whilst lower mean

Table 2 Demographic characteristics of the sample

	AQol-4D completers	AQoL-4D non-completers	*p* value
	n = 221	*n* = 47	
Age, mean ± SD	52.7 ± 14.2	53.6 ± 13.2	0.694
Sex (male)	41.6 %	41.3 %	0.552
Relationship status:			
currently married/defacto	79.6 %	68.1 %	0.066
Country of birth:			
Australia	83.7 %	85.1 %	0.506
United Kingdom	9.0 %	8.5 %	0.584
Highest level of education completed[a]:			
< yr 12	24.7 %	25.0 %	0.565
certificate, Trade etc.	31.7 %	39.4 %	0.245
yr 12	10.4 %	3.0 %	0.149
university	35.7 %	33.3 %	0.476
Labour force participation:			
employed full time	32.1 %	17.0 %	0.026
employed part-time	15.4 %	14.9 %	0.568
self-employed	9.0 %	10.6 %	0.455
retired	25.3 %	19.1 %	0.242
Unemployed	5.4 %	4.3 %	0.542

[a]For this question, *n* = 33 for the non-completer group

HSUV were reported for female participants for each category, these differences were not significant.

To investigate the impact of symptomatic HH on utility, the four categories of HH were combined into asymptomatic (categories 1 and 2), and symptomatic (categories 3 and 4) participants. Utility was significantly lower for the symptomatic group for males (0.85 v. 0.59: H = 25.36, $p < 0.001$), females (0.75 v. 0.58: H = 14.90, $p < 0.001$) and overall (0.80 v. 0.58: H = 38.79, $p < 0.001$) (Table 5).

In keeping with these findings, evaluation of the impact of HH related comorbidities on utility found all comorbidities were related to lower mean utility than reported for participants reporting no comorbidities (0.76) and the entire HH cohort (0.66) (Table 6). Using the sample mean utility value as the reference case (0.66), participants self-reporting arthritis related to HH had a lower mean utility (0.52: F(1,198) = 10.854, $p = 0.001$). Whilst lower mean utility values were reported for fibrosis, cirrhosis, heart

Table 3 Comparison of HH cohort and Australian population normative utility values [23]

Variables	Mean HSUV	95 % CI	n	Males			Females			Population norm HSUV	95 % CI
				Mean HSUV	95 % CI	n	Mean HSUV	95 % CI	n		
Age group:											
20–29	0.67	0.55–0.80	10	0.75	0.53–1.00	2	0.65	0.49–0.70	8	0.86	0.85–0.87
30–39	0.72	0.62–0.80	30	0.78	0.66–0.90	7	0.70	0.59–0.81	23	0.84	0.83–0.85
40–49	0.66	0.57–0.74	39	0.72	0.57–0.84	15	0.62	0.50–0.74	24	0.81	0.80–0.82
50–59	0.63	0.54–0.70	52	0.62	0.47–0.75	19	0.63	0.54–0.71	33	0.80	0.78–0.81
60–69	0.67	0.61–0.73	67	0.70	0.62–0.78	34	0.65	0.54–0.74	33	0.80	0.78–0.81
70–79	0.61	0.47–0.73	16	0.63	0.47–0.76	11	0.56	0.21–0.92	5	0.76	0.76–0.79
Sex											
Male	0.69	0.64–0.75	92							0.82	0.81–0.83
Female	0.64	0.60–0.69	129							0.81	0.80–0.81
All	0.66	0.63–0.70	221							0.81	0.81–0.82

Note: HSUV refers to health state utility values; 95 % CI refers to the 95 % confidence interval

Table 4 Mean utility values by categories of HH by sex

Categories of HH	HSUV mean	SD	n	95 % CI
All participants				
Category 1	0.76	0.21	20	0.67–0.85
Category 2	0.81	0.18	63	0.76–0.85
Category 3	0.60	0.27	115	0.55–0.66
Category 4	0.50	0.27	23	0.39–0.61
All categories	0.66	0.26	221	0.63–0.70
Males				
Category 1	0.88	0.10	6	0.78–0.98
Category 2	0.85	0.12	29	0.80–0.89
Category 3	0.59	0.28	45	0.51–0.68
Category 4	0.59	0.23	12	0.44–0.74
All categories	0.69	0.27	92	0.64–0.75
Females				
Category 1	0.71	0.24	14	0.58–0.84
Category 2	0.77	0.21	34	0.70–0.85
Category 3	0.60	0.26	70	0.54–0.66
Category 4	0.41	0.29	11	0.22–0.60
All categories	0.64	0.26	129	0.60–0.69

Note: HSUV refers to health state utility values; SD standard deviation; 95 % CI refers to the 95 % confidence interval

failure, cardiomyopathy, diabetes and porphyria cutanea tarda, only small numbers of participants reported these co-morbidities, therefore these should be interpreted with caution (Table 6).

Participants were also asked to report on experience of symptoms related to HH and iron overload in the preceding three months (Table 7). Participants were asked if they thought these symptoms were related to HH, possibly related or not related. Only participants reporting their symptoms to be related to HH were included to minimise over-reporting. Of a maximum of 20 symptoms and conditions, the median number experienced by the sample was 3 (SD = 3.8, range 0–15). When compared with the reference HSUV, all symptoms were associated with lower utility. A Pearson correlation coefficient was calculated to assess the relationship between symptom count and HSUV, and a strong negative correlation was found ($r = -0.685$; $p < 0.001$) (Fig. 1).

Discussion

This is the first study that reports HSUV measured directly from a cohort with HH. This is of importance, as a lack of robust health economic data has been cited as a barrier to implementing population screening programs for HH [25, 30, 31, 42]. The utility values calculated in this study provide robust estimates that can be used in future economic models of screening interventions. Whilst the sampling strategy may have introduced bias, this has been mitigated by reporting utility values for categories of HH rather than across the study population in general. These values can then be used in combination with penetrance rates in economic models for HH interventions.

Symptomatic stages of HH (categories three and four [25]) were associated with lower utility than asymptomatic stages. The values for all four categories are useful, as they incorporate all aspects of HH and related conditions and can be used to populate health economic models. Previous CUA models have only incorporated specific comorbidities which are associated with significant morbidity and mortality: cirrhosis, diabetes and heart failure, with no consideration of common comorbidities such as arthritis, or symptoms such as fatigue. This may be related to the relatively high prevalence of both fatigue and arthritis amongst other populations,

Table 5 Mean utility values of symptomatic HH

Categories of HH	HSUV mean	SD	n	95 % CI	Between groups[a]
All participants					
Categories 1 & 2	0.80	0.19	83	0.76–0.84	$H = 38.79$, $p < 0.001$
Categories 3 & 4	0.58	0.27	138	0.54–0.63	
All categories	0.66	0.26	221	0.63–0.70	
Males					
Categories 1 & 2	0.85	0.11	35	0.82–0.89	$H = 25.36$, $p < 0.001$
Categories 3 & 4	0.59	0.27	57	0.52–0.67	
All categories	0.69	0.26	92	0.64–0.75	
Females					
Categories 1 &2	0.75	0.22	48	0.69–0.82	$H = 14.90$, $p < 0.001$
Categories 3 & 4	0.58	0.27	81	0.52–0.64	
All categories	0.64	0.64	129	0.60–0.69	

Note: HSUV refers to health state utility values; SD standard deviation; 95 % CI refers to the 95 % confidence interval
[a]Kruskal Wallis one way analysis of variance was used for this test for significance

Table 6 Mean utility values by self-reported HH-related comorbidities

HH-related comorbidities[a]	mean HSUV	SD	n
All participants			
no comorbidity	0.76	0.21	100
arthritis	0.52	0.25	35
fibrosis	0.53	0.29	7
cirrhosis	0.61	0.31	5
heart failure	0.58	0.24	3
cardiomyopathy	0.30	-	1
diabetes	0.52	0.33	4
porphyria cutanea tarda	0.02	-	1
Males			
no comorbidity	0.76	0.25	39
arthritis	0.59	0.23	15
fibrosis	0.69	0.05	5
cirrhosis	0.74	0.16	3
Females			
no comorbidity	0.76	0.19	61
arthritis	0.48	0.26	20
fibrosis	0.12	0.02	2
cirrhosis	0.42	0.45	2

Note: HSUV refers to health state utility values; SD standard deviation
[a]Participants were asked if they had been diagnosed with these conditions and that they were considered to be related to HH and iron overload. Participants with these conditions, but were unsure if they were related to HH were not included in this analysis

and the difficulties surrounding the aetiologies of both, however there is evidence suggesting that the prevalence of both is higher amongst some groups of HH patients. The prevalence of fatigue amongst general practice patients has been estimated to be between 1.4 and 7.0 % of encounters [43–46]. Work by Allen and colleagues has reported a much higher rate of 22 % for C282Y homozygotes with elevated serum ferritin levels (greater than 1,000 μg/l) [10]. Similarly, arthritis, specifically osteoarthritis, is prevalent in Australia, with 9 % reporting this condition [47]. Allen and colleagues reported use of arthritis medication as a proxy measure for arthritis, noting that 20 % of C282Y homozygotes with serum ferritin greater than 1,000 μg/l reported use of these medications. In combination, these data guided the decision to include arthritis and fatigue in the current study.

To date, just four cost utility analyses have been published on HH screening programs, none of which cited the sources of the utility values employed [7, 48–50]. Values were assigned for cirrhosis, diabetes and heart failure, and in some cases, combinations of these. In a Norwegian study [48], a basal utility value of 1.00 was assumed for all HH conditions except cirrhosis, which was assigned a utility of 0.95, values that are substantially higher than those reported here. Two Canadian studies, by the same research group, used utilities of 0.8 for cirrhosis, 0.9 for diabetes, 0.5 for heart failure, 0.72 for cirrhosis and diabetes, 0.78 for cirrhosis and heart failure, 0.87 for diabetes and heart failure and 0.70 for a combination of cirrhosis, diabetes and heart failure [7, 49]. A fourth study did not provide the utility values used in the modelling [50]. Some concerns arise in respect of these estimates. First, in comparing these utility values to US population normative data, a disparity appears: the mean utility derived from the SF-6D ranged from 0.79 to 0.81 for persons aged 35 to 74, and similarly, using the EQ-5D, mean utility ranged between 0.87 and 0.89 [51]. The fact that the utility estimates that were used in cost utility analyses for participants with health conditions such as cirrhosis and diabetes are similar to or higher than those reported for the general US population indicates these estimates may be incorrect. The likely overestimates of HSUV for HH-related conditions are likely to lead to underestimates of potential utility gains associated with screening interventions.

Second, disease specific HSUV used in these cost utility analyses are also higher than suggested in published literature. A meta-analysis of utility values for liver diseases using a range of approaches to measure utility reported a mean of 0.75 for compensated cirrhosis (range 0.65–0.90) and 0.67 for decompensated cirrhosis (range 0.57–0.81) [52]. Whilst our study did not differentiate cirrhosis in this manner, amongst the small number of participants reporting this condition ($n = 5$), the mean utility (0.61) was slightly lower than reported for decompensated cirrhosis but within the range reported. In contrast, the published cost utility analyses used values of 0.95 [48] and 0.8 [7, 49], higher than the mean values reported for both compensated and decompensated cirrhosis [52]. Similarly, a meta-analysis of utility values for diabetes reported a mean of 0.76 (range 0.53–0.88) [53]. In our study, a mean of 0.52 was reported ($n = 4$), slightly lower than the lower range reported in this meta-analysis. In the three HH cost utility analyses, one used a utility value for diabetes of 1.00 [48], and two used a value of 0.9 [7, 49], both notably higher than published estimates.

Mean utility for heart failure varies depending on the severity of the condition. From a large, multi-site trial that used the EQ-5D, mean utility for different levels of severity based on the New York Heart Association (NYHA) classifications were: class I: 0.815, class II: 0.720, class III: 0.590, class IV: 0.508 [54]. Our study reported a mean of 0.58, however data were available for only three participants, and all were in different NYHA classes. The two Canadian CUA models used a utility value of 0.5 [7, 49], which is similar to the NYHA class 4. In contrast, the Norwegian study assumed a

Table 7 Mean utility values for HH related symptoms

Experienced in the last 3 months	mean HSUV	SD	n	Males			Females		
				mean HSUV	SD	n	mean HSUV	SD	n
General effects									
Chronic fatigue	0.55	0.29	102	0.56	0.31	37	0.55	0.29	65
Weakness	0.49	0.26	87	0.51	0.28	33	0.48	0.26	54
Unexplained weight loss	0.42	0.40	10	1.00	-	1	0.35	0.36	9
Unexplained weight gain	0.50	0.26	30	0.37	0.31	8	0.55	0.23	22
Liver disease									
Abdominal swelling	0.40	0.25	35	0.41	0.33	9	0.39	0.22	26
Abdominal pain/discomfort	0.47	0.26	47	0.51	0.31	12	0.46	0.25	35
Enlarged liver (hepatomegaly)	0.40	0.24	15	0.57	0.19	6	0.29	0.21	9
Cardiac-related problems									
Swelling of feet and/or ankles	0.46	0.23	47	0.43	0.24	17	0.48	0.22	30
Shortness of breath- walking quickly or uphill	0.50	0.27	64	0.54	0.27	24	0.48	0.26	40
Shortness of breath- walking on level ground	0.36	0.26	29	0.39	0.26	14	0.33	0.27	15
Shortness of breath- resting in a chair	0.31	0.25	8	0.32	0.45	3	0.21	0.24	5
Heart failure or weak heart	0.30	-	1	0.30	-	1	-	-	-
Abnormal heart rhythm/ arrhythmia	0.55	0.23	25	0.61	0.17	8	0.52	0.26	17
Heart disease	0.52	0.27	6	0.49	0.28	5	0.71	-	1
Arthritis									
Swollen/tender metacarpophalangeal joints (fingers/hands)	0.48	0.25	58	0.47	0.30	21	0.49	0.22	37
Other joint stiffness/pain/ache	0.55	0.26	96	0.6	0.26	39	0.51	0.24	57
Skin changes									
Change in skin colour	0.45	0.29	25	0.50	0.35	8	0.43	0.27	17
Increased facial hair growth	0.32	0.21	14	-	-	-	0.32	0.21	14
Reproductive									
Loss of libido and/or erectile dysfunction	0.49	0.27	49	0.48	0.27	17	0.49	0.28	32
Unexplained confusion and/or memory loss	0.40	0.24	53	0.39	0.25	18	0.41	0.24	35

Note: HSUV refers to health state utility values; SD standard deviation

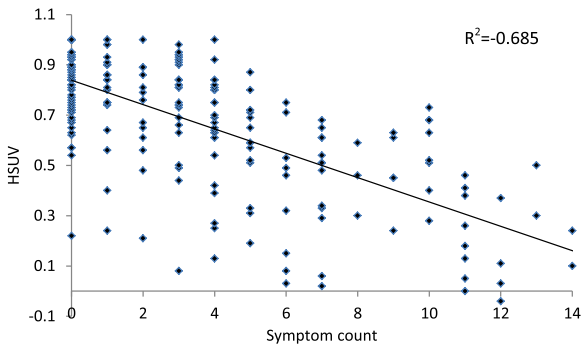

Fig. 1 Linear regression of HSUV and symptom count related to HH

utility of 1.00, which is not in keeping with estimates in the current literature [48].

To date, no economic analysis has incorporated HSUV related to arthritis. This is surprising as arthritis related to iron overload is commonly reported amongst patients diagnosed with HH [10, 55–57]. Whilst HRQoL is not synonymous with HSUV, it can serve as an indicator. A study examining the effects of a range of HH-related comorbidities using the SF-36 found that, compared to cirrhosis and diabetes, arthritis was the single strongest factor that impacted on HRQoL [58]. Whilst the paper was published in 1996, no subsequent studies have incorporated utility values for arthritis. Hawthorne and colleagues, using the AQOL-4D, reported the Australian normative utility value for arthritis as 0.69 (SD 0.26). Our study reported a lower mean value of 0.52 (SD 0.25, $n = 35$). In the current study, both self-reported diagnosis of arthritis related to HH and symptoms suggestive of arthritis were associated with lower

mean utility than the sample mean (0.52, 0.48, 0.66 respectively).

Limitations of this study include cross-sectional design and use of convenience sampling. Convenience sampling, which was used as a result of available resourcing, may limit the generalizability of these results. Further, the majority of the respondents were female, despite higher penetrance amongst males. To minimise sampling bias, we have focused on utility values for categories of disease and symptomatology for males and females separately. Whilst an overall sample mean HSUV is likely to be affected by under- or over-reporting from participants with more health problems, the mean values for each category are not affected. This allows for these values, in combination with penetrance estimates from robust epidemiological studies, to be used in HH health economic models.

A further limitation of this study was the reliance on participants' self-report regarding experience of HH related comorbidities and symptoms. Whilst participants were asked if the comorbidities were related to HH, even with clinical verification, it is difficult to be certain of the aetiology of these. Whilst it can be argued that there may be some over-reporting of symptoms and comorbidities believed to be caused by HH, to minimise this possibility, cases in which participants were unsure of the aetiology have been excluded. Symptoms and comorbidities were only included when participants stated that they were related to HH. Lastly, the small number of participants reporting HH-related comorbidities was also a limitation. Whilst utility values were calculated wherever possible, the small number of respondents means that these data should be interpreted with caution and that no meaningful comparisons can be made between these comorbidities.

Conclusions

In conclusion, this is the first study to report utility values measured directly from people with HH. Despite study limitations, these values are the best available to date, and can be used to populate health economic models investigating the cost utility of HH interventions.

Competing interests

Barbara de Graaff, Amanda Neil, Kristy Sanderson, Kwang Chien Yee, and Andrew J. Palmer have no financial or non-financial competing conflicts of interest to declare that are directly relevant to the content of this manuscript.

Authors' contributions

BdeG: planning of study, development of survey, ethics submission, recruitment, data analysis, preparation of manuscript. AN: contributed to study design, assisted with preparation of manuscript, statistics advice. KS: contributed to study design, assisted with preparation of manuscript. KCY: contributed to study design, assisted with preparation of manuscript, provided medical opinion; AP: planning of study, contributed to study design and development of survey, assisted with preparation of manuscript. All authors read and approved the final manuscript.

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Date ____/_____/ 20___

Email address: _____

Your email address will only be used to send you the link to the follow-up cost diaries. It will not be used for any other purpose.

DEMOGRAPHICS

1a. What is your date of birth? ____/____/_____

1b. What is your sex?

Male……..0
Female……1

1c. What is your postcode? _____

1d. What is your current relationship status?

Currently single, never married……..0

Currently married or defacto……1

Currently separated, divorced or widowed….2

1e. What country were you born in?_____

1f. What is your ancestry/ethnicity (mark all that apply)?

We are interested in ethnicity as haemochromatosis mostly occurs in people of European ancestry. We would like to explore this in the current study.

Australian Aboriginal……0

Australian (Caucasian)……1

Chinese……2

Czech……3

Danish……4

Dutch……5

English……6

Finnish……7

French……8

German……9

Greek……10

Torres Strait Islander……11

Indian……12

Irish……13

Italian……14

Kurdish……15

Lebanese……16

Maori……17

New Zealand……18

Norwegian……19

Polish……20

Scottish……21

Spanish……22

Vietnamese……23

Welsh……24

Other (please specify)_____

HOME ENVIRONMENT

The following questions are to provide information on the support you have within your home and if other people are dependent on you for support

2a. Which of the following best describes your usual residence? (Please mark one only)

I live with my spouse or partner without children……..0
I live with my spouse or partner with children……1
I live only with my children……2
I live with one of my parents (without children of my own)……3
I live with both of my parents (without children of my own)……4
I live with one of my parents with child(ren) of my own……5
I live with both of my parents with child(ren) of my own……6
I live with at least one friend, or other people like flatmates in a group household……7
I live with other people in a hostel or nursing home environment……8
I live on my own……9
I live with at least one family member (eg sibling, aunt, uncle)……10
Other (please specify)_____.....11

2b. Please select the following option that best describes the living environment (Please mark one only)

Public rented house/unit……0
Private rented house/unit……1
Family home……2
Own home/unit……3
Supported accommodation……4
No fixed address (i.e. homeless)……5
Institution/hospital……6
Other (eg caravan), please specify:_____

2c. If you have people who rely on you (eg school children or elderly relatives), please write down the number of these people.

Children at home and/or still in education _____
Elderly relatives _____
Spouse/partner _____

EMPLOYMENT

The following questions are about your employment, and the impact haemochromatosis related health problems may have had on your employment.

3a. Which of the following <u>best</u> describes you <u>current</u> employment status? (mark one only)

Employed full-time……0

Employed part-time……1

How many hours per week on average do you work? _____*hours*

Self-employed……2

How many hours per week on average do you work? _____*hours*

Unemployed, seeking full-time paid employment……3

Unemployed, seeking part-time paid employment……4

Unemployed, not seeking paid employment……5

Unpaid work only (eg home management work)……6

Unpaid work only (eg volunteer work)……10

Student……7

Retired, <u>not</u> on a government pension (ie self-funded retiree)……8

What age did you retire? _____*years*

Did you receive a disability payout? (please circle) Yes No

Retired, on a government pension……9

What age did you retire? _____*years*

Did you receive a disability payout? (please circle) Yes No

3ai). Do you currently receive any of these government pensions or allowances? (Which ones?)

No……0
Abstudy……1
Age pension……2
Austudy……3
Bereavement allowance……4
Carer allowance……5
Carer payment……6
CDEP participant supplement……7

Child care benefit……8
Child care rebate……..9
Dad and partner pay……..10
Disability support pension……11
Family tax benefit part A……12
Family tax benefit part b……13
Income support bonus ……14
Jobs education and training child care fee assistance……15
Low income family supplement……..16
Low income supplement……17
Mobility allowance……..18
Newstart allowance……..19
Parental leave pay ……..20
Parenting payment……21
Partner allowance……..22
Pensioner education supplement……23
Remote area allowance……24
Sickness allowance……26
Single income family supplement……27
Special benefit……28
Widow allowance……..29
Widow B pension……..30
Wife pension……31
Youth allowance……32

3aii) Do you have a type of Concession or Health Care Card? *(select all that apply)*

No……0
Yes, Pensioner Concession Card……1
Yes, Commonwealth Seniors Health Card……2
Yes, Low Income Health Care Card……3
DVA Gold card……4
DVA White card……5
DVA Orange card……6
Yes, other *(please specify)*_____...7

3b. Have you experienced any symptoms related to your haemochromatosis, including fatigue, arthritis, diabetes, heart disease, liver disease or any other health problems?

Yes……1
No……..0 (skip to Q3c)

3bi. Please state what your occupation is NOW and what it was BEFORE the onset of symptoms related to your haemochromatosis, even if it's the same as now.
Please complete this whether or not you are currently employed.

Please note these are Australian Bureau of Statistics categories, please read carefully before choosing.

	Now	**Before symptoms**
Managers or Administrators: Legislators and government appointed officials; general and specialist managers; farm managers; Commissioned Officers at management level		
Professionals: Professionals that are not managers or administrators; Such as: engineers, architects, doctors, research scientists, veterinarians, lawyers, registered nurses, accountants, auditors, analysts….		
Associate professionals: Associates and technicians in engineering and science; dealers and traders in finance; shop, outlet or customer service managers; sales, real estate and travel agents; chefs; managers in hospitality; health, welfare and police officers; sports players and coaches or officials		
Trade persons and related workers: Skilled agricultural and horticultural workers; mechanical and fabrication engineering; tradespersons in automotive, electrical, electronics, construction, and food		
Advanced clerical and services workers: Secretaries, personal assistants and advanced clerical service workers….		
Intermediate clerical, sales and service workers: Intermediate clerical, sales and service and related workers		
Intermediate production and transport workers: Intermediate plant operators, machine operators, road and rail transport drivers, other intermediate production		
Elementary clerical, sales and service workers: Elementary clerical, sales and service workers		
Labourers and related workers: Cleaners, factory labourers, other labourers and related workers		
Other: Home duties		
Student		
Retired		

Voluntary work		
Unemployed		
Other (please specify)_____		

3bii. If you indicated a change in occupation has occurred since you have experienced haemochromatosis-related health problems, was this change related to these?

Yes……1

No……..0

3c. What is your main source of income?

Wage/salary……0

Superannuation……..1

Government benefit……2

Other……3 (Please specify)_____

3ci. Which of the following is your current gross (before tax) <u>personal</u> income? (please mark only one)

nil income……10

$1 - $199 per week (less than $10,399 per year)……..0

$200 - $299 per week ($10,400 - $15,599 per year) ……1

$300 - $399 per week ($15,600 - $20,799 per year)……2

$400 - $599 per week ($20,800 - $31,199 per year)……3

$600 - $799 per week ($31,200 - $41,599 per year)……4

$800 - $999 per week ($41,600 - $51,999 per year)……5

$1,000 - $1,249 per week ($52,000 - $64,999 per year)……6

$1,250 - $1,499 per week ($65,000 - $77,999 per year)……7

$1,500 - $1,999 per week ($78,000 - $103,999 per year)……8

$2,000 – or more per week ($104,000 or more per year)……..9

3cii.Which of the following is your current gross (before tax) <u>combined household</u> income? (please mark one only)

nil income……10

$1 - $199 per week (less than $10,399 per year)……..0

$200 - $299 per week ($10,400 - $15,599 per year) ……1

$300 - $399 per week ($15,600 - $20,799 per year)……2

$400 - $599 per week ($20,800 - $31,199 per year)……..3

$600 - $799 per week ($31,200 - $41,599 per year)……..4

$800 - $999 per week ($41,600 - $51,999 per year)……..5

$1,000 - $1,249 per week ($52,000 - $64,999 per year)……..6

$1,250 - $1,499 per week ($65,000 - $77,999 per year)……..7

$1,500 - $1,999 per week ($78,000 - $103,999 per year)……..8

$2,000 – or more per week ($104,000 or more per year)……..9

3d. What is the highest level of education you have <u>completed</u>?

Did not go to school……0
Year 8 or below……..1
Year 9 or equivalent……..2
Year 10 or equivalent……3
Year 11 or equivalent……..4
Year 12 or equivalent……5
Trade certificate……6
Certificate II……7
Associate diploma……8
Advanced diploma ……9
Bachelor degree……10
Postgraduate degree……..11

3di. Has having haemochromatosis-related health problems made you <u>leave</u> your education?

Yes……1

No……..0 *skip to 3e*

3dii. If yes, in what year did you have to leave? _____

3e. Has having haemochromatosis-related health problems made you <u>leave</u> your paid employment?

Yes……1

No……..0 *skip to 3f*

3ei. If yes, in what year did you have to leave? _____

3eii. What were the main reasons you left paid employment? (can mark more than one)

Organisational factors

Not allowed flexible work hours/work conditions (eg work from home)……0

Not considered for promotion (perceived discrimination)……1

Ran out of paid sick leave……2

More suitable work not able to be found within the same organisation ……3

Asked to leave/sacked……4

Getting to/from work

Unable to get to/from work……5

Unable to obtain appropriate parking (eg close to work)……6

Unable to get up and dressed for work……7

Unable to get dressed in time for work……8

Getting around at work

Architectural barriers (eg stairs)……9

General area accessibility……10

Use of equipment at work

Difficulty with use of necessary equipment……11

Difficulty in standing for long periods to use equipment……12

Chair/desk inappropriate for comfort and support……13

Impact of physical symptoms

Fatigue/tiredness……14

Joint pain……15

Abdominal pain……16

Shortness of breath……17

Swelling of feet and/or ankles……18

Difficulty with performing work due to other symptoms

Please specify _____.....19

Other reasons

Feel the people at work are critical of unhelpful or unsympathetic……20

Feel as if I'm not doing a good enough job according to my own standards…….21

Feel as if I'm a burden to my colleagues……22

Feel to stressed by the effort involved with maintain work……23

Doctor or health professional advised……24

Other _____

3f. Has having haemochromatosis-related health problems made you <u>reduce</u> the hours of your paid employment?

Yes……1

No……0 *(skip to Q4a)*

Not applicable……2 *(skip to Q4a)*

3fi. If yes, in which year did this occur? _____

3fii. How many hours were you engaged in employment prior to reducing your hours?

_____hrs

3fiii. How many hours are you engaged in paid employment now?

_____hrs

PERSONAL SUPPORT

The following questions are about the assistance you may receive or need from people that you do not pay for yourself. The assistance you receive or need is because of your haemochromatosis related health conditions, such as fatigue, arthritis, diabetes, liver or heart disease.

4a. Following is a list of items you may receive or need assistance for because of your haemochromatosis-related health problems. Please report an estimate for the hours of assistance you receive or need per week, for each item.

		Do not pay for service					Estimate the number of hours of additional support you need but do not receive
		Report hours of assistance provided per week					
	N/A	Partner/ spouse	Other relative	Friend	Volunteer	Non-charging organisation	
Activities of daily living (eg personal care, meal preparation, physical access to or within the home)							
Home and garden (eg essential household tasks; repairs and maintenance; bills and household paperwork; maintenance outside and garden)							
Essential transport							
Child care							
Other (please specify)							

4b. Has someone (e.g. partner, friend) been absent from their paid employment to help you with your haemochromatosis related health problems (e.g. support with attending appointments or collecting medications, caring for you at home)?

Yes……..1

No……..0 *(skip to Q4c)*

4bi. In the last 4 weeks, how many hours/days has this person/s been absent for work to provide support to you, which was in relation to your haemochromatosis related health problems (e.g. arthritis, diabetes, liver disease, heart disease)?

_____hours

_____days

4c. Has someone (e.g. partner, friend) changed their employment situation or conditions to help you with your haemochromatosis-related health problems?

Yes……..1

No……..0 *(skip to Q5a)*

4ci. If yes, who? (eg partner, child, parent)_____

4cii. Please complete for your support person's change in employment:

Average hours per week worked previously _____hrs

Average hours per week worked currently _____hrs

Average earnings per week previously $_____

Average earnings per week currently $_____

Other change in location or type of work (please specify) _____

4ciii. Does this person receive a carer's payment or allowance from the government in relation to the care they provide you?

No……..0

Yes, carer's payment……..1

Yes, carer's allowance……2

Don't know……3

INSURANCE

These next questions ask about any health insurance you may have, and changes to this due to your haemochromatosis.

5a. Do you <u>currently</u> have Private Health insurance?

Yes……..1

No……..0*(skip to Q5b)*

5ai. If yes, what level of cover do you have:

Hospital only……0
Extras only……1
Hospital and extras ……..2
Other……..3 *specify*_____

5b. Have you changed your private health insurance cover because of your haemochromatosis-related health problems?

Yes……..1

No……..0 *(skip to Q6a)*

5bi. If yes, what were the reason(s)

Can't afford premiums so decreased level of cover……..0
Can't afford premiums so stopped cover……1
Don't believe the benefit is worth the cost of the premiums……..2
Don't believe I need it now……3
Started cover so did not have to be on waiting list……..4
Increased level of cover so receive benefits for more services……5
Other (please specify)_____.....6

5bii. What was the level of care you <u>used to have</u>?

No cover……..0
Hospital only……..1
Extras only……..2
Hospital and extras……..3
Other……..4

HAEMOCHROMATOSIS RELATED HEALTH

The next set of questions asks you about your health.

6a. In what year were you told you had haemochromatosis? _____

6b. How were you diagnosed with haemochromatosis?

Family member diagnosed, so I got tested……..0

GP tested because I had symptoms ……1

GP tested, but I didn't have symptoms……..2

Specialist Dr tested because I had symptoms……3

Specialist Dr tested, but I didn't have symptoms……4

Other *specify*_____

6c If you remember the result of you iron level blood tests when you were first diagnosed, please

specify what it was.

This may include transferrin, ferritin, iron levels and/or total iron-binding capacity. Please provide as much information as you can.

_____

_____

_____

6d. Have you had a genetic test for haemochromatosis?

Yes……..1

No……..0 *(skip to Q6e)*

6di. If yes, what was the result?

C282Y Homozygote……0

C282Y/H63D compound heterozygote……1

H63D Homozygote……2

S56C Homozygote……3

S56C/C282Y compound heterozygote……4

S56C/H63D compound heterozygote……5

Other……..6

Declined……8

Don't know/can't remember……7

6e. Some doctors and researchers have suggested there are 4 main categories/stages of haemochromatosis. Please indicate the category you would be in:

Please note there is no evidence to suggest that people with haemochromatosis will progress through all of these stages. In fact, early treatment means haemochromatosis is unlikely to cause any health problems.

1. Genetic mutation ONLY, no health problems related to haemochromatosis……0

2. Iron overload ONLY (raised serum ferritin and/or transferrin saturation)……1

3. Iron overload AND early symptoms (fatigue and arthritis)……..2

4. Iron overload AND organ damage (such as diabetes, liver diseases, heart disease)….3

6f. The following questions will ask if you have ever been diagnosed with a range of health conditions, and if they were/are related to your haemochromatosis.

		No	Yes, related to haemochromatosis	Yes, but not related to haemochromatosis	Yes, but not sure if this is related to haemochromatosis	Year of diagnosis
Liver disease:	Fibrosis					
	Cirrhosis					
	Carcinoma (cancer)					
Heart disease	Heart failure					
	Cardiomyopathy					
	Other (please specify)					
Arthritis						
Diabetes						
Porphyria cutanea tarda (Increased growth of hair on face)						

6g. The list below includes several effects and complications of haemochromatosis and iron overload. Please indicate if you have experienced any of these in the past 3 months AND they were (or were likely to be) related to your haemochromatosis.

	Experienced in the last 3 months
General effects Chronic fatigue	
Weakness	
Unexplained weight loss	
Unexplained weight gain	
Liver disease Abdominal swelling	
Abdominal pain/discomfort	
Enlarged liver (hepatomegaly)	
Diabetes	
Heart-related problems Swelling of your feet and/or ankles	
Shortness of breath- walking quickly or uphill	
Shortness of breath- walking on level ground	
Shortness of breath- resting in a chair	
Heart failure or weak heart	
Abnormal heart rhythm/ arrhythmia	
Heart disease	
Arthritis Swollen/tender metacarpophalangeal joints (fingers/hands)	
Other joint stiffness/pain/ache	
Skin changes Change in skin colour	
Increased facial hair growth	
Hypogonadism Loss of libido, erectile dysfunction	
Unexplained confusion and/or memory loss	
Other (please specify)	

Charlson Comorbidity Index

7a. As far as you know, do you have any of the following health conditions at the present time (tick all that apply):

	Yes
Asthma, emphysema, or chronic bronchitis	
Arthritis or rheumatism	
Cancer, diagnosed in the past 3 years	
Diabetes	
Digestive problems (such as ulcer, colitis, or gallbladder disease)	
Heart trouble (such as angina, congestive heart failure, or coronary artery disease)	
HIV illness or AIDS	
Kidney disease	
Liver problems (such as cirrhosis)	
Stroke	

Heart Disease

Q8. Have you ever been diagnosed with heart disease related to your haemochromatosis?

Yes……1

No……0 *(skip to Arthritis section)*

Q8a. These questions are related to the impact heart disease has on your day to day health.

Please tick one box ONLY.

	Tick **ONE** box only
I can perform all physical activity without getting short of breath, tired or having palpitations	
I get short of breath or tired, or have palpitations when performing more strenuous activities, eg walking on steep inclines or walking up several flights of steps	
I get short of breath or tired, or have palpitations when performing day to day activities, eg walking on the flat	
I feel breathless at rest and am mostly housebound. I am unable to carry out any physical activity without getting short of breath or tired, or having palpitations	

Arthritis

Q9. Have you ever been diagnosed with arthritis related to your haemochromatosis?

Yes……1

No……0 *(skip to Diabetes section)*

Assessment of Pain

Please answer the following question by placing a mark through the horizontal line.

9a. On this line, in your <u>left fingers</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9b. On this line, in your <u>left wrist</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9c. On this line, in your <u>left elbow</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9d. On this line, in your <u>left shoulder</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9e. On this line, in your <u>left hip</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9f. On this line, in your <u>left knee</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

his line, in your <u>left ankle</u>, where would you rate your pain? U /s as a time frame.

None ——————————————— **Unbearable**

9h. On this line, in your <u>left toes</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9i. On this line, in your <u>neck,</u> where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9j. On this line, in your <u>right fingers</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9k. On this line, in your <u>right wrist</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9l. On this line, in your <u>right elbow</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9m. On this line, in your <u>right shoulder</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9n. On this line, in your <u>right hip,</u> where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9o. On this line, in your <u>right knee</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9p. On this line, in your <u>right ankle</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————— **Unbearable**

9q. On this line, in your <u>right toes</u>, where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————————— **Unbearable**

9r. On this line, in your <u>back,</u> where would you rate your pain? Use the last 30 days as a time frame.

None ——————————————————— **Unbearable**

Diabetes

Q10. Have you ever been diagnosed with diabetes related to your haemochromatosis?

Yes……1

No……0 *(skip to 11a)*

Diabetes related to HH:

10a. In what year were you diagnosed with diabetes? _____

10b. Have you experienced any of the following complications due to diabetes:

	Yes
Eyes: Macular oedema	
Nonproliferative retinopathy	
Proliferative retinopathy	
Laser therapy	
Blindness	
Kidneys: Microalbuminuria	
Macroalbuminuria	
End stage renal disease (dialysis or kidney transplant)	
Neuropathy Peripheral neuropathy: Numbness/tingling or pain in toes, feet, legs, hands, arms or fingers	
Foot ulcers	
Autonomic neuropathy	
Proximal neuropathy	
Focal neuropathy	
Amputation: *toe/s*	
foot	
below knee	
above knee	

other	
Cardiovascular disease Coronary artery disease/angina	
Myocardial infarction	
Stroke/TIA	

OTHER HEALTH PROBLEMS

11a. Apart from any haemochromatosis related health problems, do you experience any other health problems?

Yes……..1

No……..0 *(skip to Quality of Life)*

If yes, please list below	**Year of diagnosis or onset**

11b. Do these conditions cause you any disability?

Yes……..1

No……..0 *(skip to Quality of Life)*

11bi. Do these conditions cause you <u>more</u> disability than your haemochromatosis-related health problems?

Yes……..1

No……..1

QUALITY OF LIFE

Tick the box next to the response that best fits your situation

aqol1. Do you need any help looking after yourself? *(For example: dressing, bathing, eating)*
☐I need no help at all.

☐Occasionally I need some help with personal care tasks.

☐I need help with the more difficult personal care tasks.

☐I need daily help with most or all personal care tasks.

aqol 2. When doing household tasks: *(For example: cooking, cleaning the house, washing)*
☐I need no help at all.

☐Occasionally I need some help with household tasks.

☐I need help with the more difficult household tasks.

☐I need daily help with most or all household tasks.

aqol 3. Thinking about how easily you can get around your home and community:
☐I get around my home and community by myself without any difficulty.

☐I find it difficult to get around my home and community by myself.

☐I cannot get around the community by myself, but I can get around my home with some difficulty.

☐I cannot get around either the community or my home by myself.

aqol 4. Because of your health, your relationships (for example: with your friends, partner or parents) generally:
☐Are very close and warm.

☐Are sometimes close and warm.

☐Are seldom close and warm.

☐I have no close and warm relationships.

aqol 5. Thinking about your relationship with other people:
☐I have plenty of friends, and am never lonely.

☐Although I have friends, I am occasionally lonely.

☐I have some friends, but am often lonely for company.

☐I am socially isolated and feel lonely.

aqol 6. Thinking about your health and my relationship with my family:
☐My role in the family is unaffected by my health.

☐There are some parts of my family role I cannot carry out.

☐There are many parts of my family role I cannot carry out.

☐I cannot carry out any part of my family role.

aqol 7. Thinking about your vision, including when using your glasses or contact lenses if needed:
☐I see normally

☐I have some difficulty focusing on things, or I do not see them sharply.
For example: small print, a newspaper or seeing objects in the distance.

☐I have a lot of difficulty seeing things.
My vision is blurred. For example: I can see just enough to get by with.

☐I only see general shapes, or am blind.
For example: I need a guide to move around.

aqol 8. Thinking about your hearing, including using your hearing aid if needed:
☐I hear normally

☐I have some difficulty hearing or I do not hear clearly.
For example: I ask people to speak up, or turn up the TV or radio volume.

☐I have difficulty hearing things clearly.
For example: Often I do not understand what is said. I usually do not take part in conversations because I cannot hear what is said.

☐I hear very little indeed.
For example: I cannot fully understand loud voices speaking directly to me.

aqol 9. When you communicate with others: (For example: by talking, listening, writing or signing.)
☐I have no trouble speaking to them or understanding what they are saying

☐I have some difficulty being understood by people who do not know me. I have no trouble understanding what others are saying to me.

☐I am only understood by people who know me well. I have great trouble understanding what others are saying to me.

☐I cannot adequately communicate with others.

aqol 10. Thinking about how you sleep:

☐I am able to sleep without difficulty most of the time.

☐My sleep is interrupted some of the time, but I am usually able to go back to sleep without difficulty.

☐My sleep is interrupted most nights, but I am usually able to go back to sleep without difficulty.

☐I sleep in short bursts only. I am awake most of the night.

aqol 11. Thinking about how you generally feel:

☐I do not feel anxious, worried or depressed.

☐I am slightly anxious, worried or depressed.

☐I feel moderately anxious, worried or depressed.

☐I am extremely anxious, worried or depressed.

aqol 12. How much pain or discomfort do you experience:

☐None at all.

☐I have moderate pain.

☐I suffer from severe pain.

☐I suffer unbearable pain.

Chapter 4: Costs associated with hereditary haemochromatosis in Australia: A cost of illness study

4.1 Preface

In the systematic review presented in Chapter 2, no literature was identified that quantified the quality of life or economic burdens associated with haemochromatosis. In the preceding chapter, data on the health state utility values were presented, clearly establishing that more severe stages of haemochromatosis are correlated with poorer quality of life, evidenced by the significantly lower utility values for these groups.

Chapter 4 presents data on the economic burden associated with haemochromatosis in Australia. A national cost of illness study was conducted to quantify the costs from the patient, government and societal perspectives. Costs included those arising from the health sector, other sector and time/productivity losses. These data establish the economic burden associated with the haemochromatosis, and can be used to populate future health economic models for haemochromatosis interventions.

This chapter has been accepted by *Australian Health Review* (Appendix 4A)

de Graaff, B., Neil, A. Sanderson K, Yee, K.C. & Palmer AJ. "Costs associated with hereditary haemochromatosis in Australia: A cost of illness study" *Australian Health Review.* Accepted for publication.

4.2 Abstract

Objective: To assess health sector, other sector and time-related (productivity) costs associated with hereditary haemochromatosis from societal, government and patient perspectives for the Australian setting.

Methods: A national web-based survey of people with haemochromatosis was conducted between November 2013 and February 2015. Participants completed a health survey and resource-use diaries. Costs were calculated using a bottom-up approach and calculated in 2015 Australian dollars.

Results: Cost data were available for 157 participants. From a societal perspective, the estimated annual cost of haemochromatosis was AUD274 million. Mean cost for symptomatic patients (AUD10,030: 95%CI 7,705-12,670) was almost three times that of asymptomatic patients (AUD3,701: 95%CI 2,423-5,296). Health sector and productivity-related time-loss were the main cost drivers. When extrapolating costs to the Australian population level, asymptomatic haemochromatosis accounted for higher costs than symptomatic haemochromatosis (AUD183 million versus 91 million), reflecting the low clinical penetrance estimate used. Total costs increased when higher clinical penetrance estimates were used.

Conclusion: This cost of illness study, the first to be published for haemochromatosis, found that whilst costs were substantial, they could be decreased by reducing clinical penetrance. Development of cost effective strategies to increase early diagnosis is likely to result in better health outcomes for patients and lower total costs.

4.3 Introduction

Hereditary haemochromatosis is a common autosomal recessive disorder amongst people of northern European ancestry [1-3]. Clinically, haemochromatosis is characterised by increased absorption of dietary iron, which is stored in the parenchymal tissues of the liver, heart and pancreas. If untreated, this can be the cause of morbidity, including type 2 diabetes, heart disease and liver disease.

Whilst several mutations of the HFE gene have been identified, C282Y homozygotes account for between 80 and 90% of morbidity and mortality [4, 5]. Other mutations are rarely observed to cause comorbidity related to iron overload [6, 7]. Between 1 in 150 to 200 people of northern European ancestry are estimated to be C282Y homozygotes; in other populations this is considerably lower to non-existent [7-12].

As iron stores increase, symptoms may progress from lethargy and arthropathy of the metacarpophalangeal joints to Type 2 diabetes, liver disease and heart disease. Symptoms of iron overload are most commonly reported in male patients aged over 30 years; symptom onset is typically later in females as menstruation reduces iron stores [7, 13, 14].

Clinical penetrance (individuals exhibiting symptoms) is incomplete and widely differing rates have been reported. For C282Y homozygotes, reported rates have varied between 2% and 76% [4, 5, 7, 8, 15-26]. This variance can in part be explained by use of different definitions of penetrance: iron studies with different iron elevation cut-off points, clinically assessed symptoms or self-reported symptoms [27]. For other common genotypes such as the H63D and S56C mutations, clinical penetrance is much lower, with some authors noting no association between the S56C allele and elevated transferrin saturation [28].

This issue of differing definitions of clinical penetrance and the resulting lack of generalizability of much of this body of research was recognised by the European Association for the Study of the Liver (EASL). In 2000, a consensus document was published outlining four categories of disease (Table 1) [27]. These categories have been adopted by a small number of other studies. One study reported penetrance of C282Y homozygosity, defined as categories 2 through to 4, as 15.8%; 12.1% for categories 3 and 4; and 2.9% for category 4

[29]. Similarly, an Australian study of a random sample of participants reported a penetrance rate, defined as categories 3 and 4, of 13.9% amongst C282Y homozygotes [8].

Table 1: Categories of haemochromatosis [27]

Category 1	Genetic mutation only (C282Y homozygotes, H63D heterozygotes and compound heterozygotes)
Category 2	Genetic mutation and elevated iron studies, either transferrin saturation or serum iron
Category 3	Genetic mutation, elevated iron levels and early symptoms, including arthritis, fatigue
Category 4	Genetic mutation, elevated iron levels and organ damage

Diagnosis and treatment of haemochromatosis are relatively straightforward. Diagnosis involves conducting serum iron studies (transferrin saturation and serum ferritin) followed by confirmatory *HFE* genotyping. Treatment consists of regular therapeutic venesection [30]. When treatment is commenced prior to irreversible organ damage, the patient retains normal life expectancy [2, 30]. As early symptoms of iron overload are non-specific, in some cases diagnosis occurs subsequent to organ damage [31, 32]. Population screening programs have been suggested to increase the rate of early diagnosis, thereby reducing morbidity and mortality associated with haemochromatosis [27, 33-35]. To date, no quantification of the costs of haemochromatosis has been published. A cost of illness (COI) study estimates all relevant costs from the perspectives of the patient, government and/or society. The preferred method is a bottom-up COI analysis that incorporates observational data [36]. This study sought to calculate the health sector, other sector and time-loss costs of haemochromatosis from the societal, government and patient perspectives for the Australian setting.

4.4 Methods

A web-based cross-sectional COI study using convenience sampling was conducted across Australia between November 2013 and February 2015. Multiple recruitment strategies were used to maximise participation: emails were sent to all members of the national haemochromatosis support group (Haemochromatosis Australia, HA) informing them of the project and the web address; a link to the survey was placed on HA's website; flyers were sent

to large Australian metropolitan hepatology, haematology and gastroenterology clinics, along with general practitioners sourced from HA's referral network. In addition, advertisements were placed on social media sites and newspaper articles about the condition and the study were published. To augment recruitment, case finding was conducted in all Tasmanian public hospitals. All patients admitted between July 2009 and June 2014 with a diagnosis of haemochromatosis, as identified in the ICD-10-AM by code E831, were sent letters by the research group, informing them of the study and inviting them to participate. Ethical approval for the study was granted by the Tasmanian Health and Medical Research Ethics Committee (H0013564).

Participants initially completed a survey on health, income, employment and health-related quality of life. This survey was followed by resource-use diaries. Participants were requested to complete the diary retrospectively for the preceding four weeks at monthly intervals over a three month period i.e. three diaries in total. The resource-use diary asked participants to only record resources used that were directly related to haemochromatosis-related health conditions, such as arthropathies, type 2 diabetes, heart disease and liver disease. For each condition, participants were then asked if it was a) related to iron overload; b) not related to iron overload; or c) unsure. Cost data were excluded if participants gave responses b or c. Resources included prescribed and non-prescribed drugs, supplements, medical appointments, medical investigations and procedures, hospitalisations (inpatient and outpatient), purchase of specialised equipment and transport costs. Data on time-related impacts, such as absenteeism, presenteeism and transfer payments related to haemochromatosis, were also collected.

4.4.1 Costing

The annual costs of haemochromatosis in Australia in 2015 have been estimated from a bottom-up, prevalence-based analysis, based on previously-reported methodologies [37, 38]. Costs were estimated by calculating an average monthly cost for each category of resource and extrapolating this to 12 months. Costs from the perspectives of the patient, government and society by EASL categories were assessed. All costs were calculated in

2015 Australian dollars (1AUD=0.75USD). An overview of the costing methodology is presented below and a full description is included in Appendix 4B.

Health sector costs

Prescribed and non-prescribed medications, supplements

Unit costs for prescribed drugs were calculated using the 2015 Pharmaceutical Benefits Scheme (PBS) Price Schedule of January 1, 2015 [39]. Frequency and dosage data were used to estimate an annual cost per participant. These costs were summed and safety net thresholds and costs were calculated based on concession card status.

Costs for non-prescribed medications and supplements were estimated by calculating the mean cost for each item based on the prices reported by three large online Australian pharmacies during January 2015 (Pharmacy Direct, Pharmacy Online, Chemist Warehouse).

Medical appointments, investigations and interventions

Costs of medical appointments (general practitioner and specialist) were calculated based on the length of the appointment, with unit costs derived from the Medicare Benefits Schedule (MBS) Book (January 1, 2015) [40]. Unit costs for all investigations were also derived from this resource. For each participant, annual expenditure was calculated, MBS safety net thresholds applied and costs calculated by perspective.

Hospitalisations

Hospitalisation costs were broken up into public and private; inpatient, outpatient and emergency only presentations. For public inpatient admissions, prices were assigned using the National Hospital Cost Data Collection cost weights for Australian Refined Diagnosis-Related Group (AR-DRG) version 6.0x, round 16 (2011-12) [41]. These costs were then adjusted for inflation using the price index for Government final consumption expenditure on hospitals and nursing homes, 2012/13 [42]. Costs for public outpatient admissions were taken from the Independent Hospital Pricing Authority [43]. For attendance at a private hospital emergency department (ED), costs were calculated by taking a sample of published costs from private hospitals and calculating the mean (no participants reported attendances at public

ED, private outpatients clinic or inpatient admissions).

Specialised equipment

Specialised equipment included use of equipment specific to haemochromatosis-related conditions, such as domestic tools for assistance with arthritis. Unit costs for these items were estimated by calculating the mean cost obtained from the three online pharmacies and specialist suppliers of equipment in February 2015. Amortisation of costs of goods with a life expectancy greater than one year was carried out [44].

Other sector costs

Transport

Transport costs were estimated by asking participants to record the distance travelled in the preceding month for haemochromatosis-related treatment. Fuel consumption was calculated using average fuel consumption for a private vehicle data from the Australian Bureau of Statistics [45]. The average national fuel price was taken from the Australian Institute of Petroleum, on April 5, 2015 [46].

Time-loss costs

Time-loss costs incorporated productivity losses from the societal perspective, and transfer costs from the government perspective [38]. Time-loss costs were not calculated from the patient perspective. A modified human capital approach was used to value time-loss costs [44]. Absenteeism was costed using questions adapted from the World Health Organization Health and Work Performance Questionnaire [47]. Mean annual number of days absent was calculated for each participant, and mean weekly earnings were taken from the Australian Bureau of Statistics for age and sex for 2013 [48]. Weekly earnings were adjusted for inflation using the Consumer Price Index (CPI) for June 2013 as the base year (102.8) and for March 2015 (106.8) [49]. Annual days absent were costed using this wage data and reported in 2015 AUD. Appendix 4B provides further explanation regarding the methodology employed.

Presenteeism (attending work when unwell) is associated with a loss of productivity and therefore incurs a cost. Participants were asked to report the number of days in the preceding month that they had attended work whilst suffering a health problem related to

haemochromatosis. Participants then provided a subjective rating of their productivity by indicating the percentage of time they were as productive as usual [50, 51]. Presenteeism was converted to days absent, with costs calculated using the same methodology for absenteeism.

Carer's time-loss costs were calculated by converting hours and/or days lost in provision of care or support for a haemochromatosis-related event to days lost. The unit cost was the mean Australian wage (2013) inflated using the March 2015 CPI [48, 49].

Transfer payments (government welfare, e.g. Disability Support Pension) to participants for haemochromatosis-related conditions were costed. Payments comprised those related to their haemochromatosis condition, cross-checked with the self-reported health conditions. Similarly, transfer payments to carers were costed depending on the form of payment received (Carer's Payment, Carer's Allowance).

4.4.2 Population cost estimates

As convenience sampling was used for this study, the sample may not be representative of all people in Australia with haemochromatosis. Assumptions used in the base case costing extrapolations were taken from the most robust datasets and studies available. Table 2 provides an overview of these.

The profile of clinical penetrance that Allen and colleagues report is comparable to EASL's categories 3 and 4 (Table 1) and used in the current study. Costs were calculated from patient, government and societal perspectives and extrapolated to the population based on these prevalence and penetrance estimates. Initially, costs were only assigned to 31% of C282Y homozygotes in Australia: an estimate of the proportion of C282Y homozygotes likely to be diagnosed through current approaches to diagnosis (cascade screening or incidental diagnosis) (L. Gurrin, Principal Investigator, HealthIron study, personal communication, March 16 2015).

Table 2: Assumptions used in base case costing calculations

Base-case assumptions	Assumptions	n
Australian population aged 20 or older [52]	-	16,652,952
Of northern European ancestry [53]	66%	10,990,948
Prevalence of C282Y homozygotes * [8]	0.68%	74,738
Diagnosed as C282Y homozygote ~	31%	23,3169
Penetrance (categories 3 and 4) [54]	13.9%	3,220

* Amongst people identifying as having Northern European ancestry

~ Either through cascade screening or incidental diagnosis (L. Gurrin, personal communication, March 16 2015).

To provide a more accurate estimate of total costs associated with haemochromatosis in Australia, costs were also estimated for the 69% of undiagnosed homozygotes. Raw cost data were recalculated by subtracting all costs for therapeutic venesection, and all costs for category 1 patients were set at zero. Other costs were maintained as it was assumed that resources would be consumed irrespective of a formal diagnosis. Assumptions in Table 2 were retained.

4.4.3 Sensitivity analyses

To reflect the variable penetrance rates reported in the literature, a sensitivity analysis around this was conducted. Penetrance estimates were varied between 1% and 50% [8, 25, 26, 52, 53] to understand how this impacts on total costs. Both diagnosed and undiagnosed C282Y homozygotes were included.

4.4.4 Statistical analysis

Simple descriptive statistics were assessed. Demographic characteristics were analysed using ANOVA and chi square. As cost data were not normally distributed, bootstrapping (x1,000) was employed to calculate 95% confidence intervals [54, 55]. Comparisons between costs are considered to be statistically significant when there is no overlap between confidence intervals. This is considered to be a conservative approach [56]. Analysis was conducted using SPSS version 22.0.0.0 and Excel for Windows.

4.5 Results

4.5.1 Demographic characteristics

Two hundred and sixty-six participants completed at least one part of the four elements of this survey: 157 completed the initial health questionnaire and at least one resource use diary, and 109 participants completed only the initial health questionnaire. Participants completing the initial survey and at least one resource use diary were included in the cost analysis.

Demographic differences between participants completing at least one resource use diary (in addition to the initial survey) and those who did not complete this were examined (Table 3). Diary-completers were older (56 yrs v. 48 yrs, $p<0.001$), and more likely to be retired from the workforce (33.6% v. 17.9%, p=0.014).

For participants included in the cost analysis, demographic characteristics were compared across EASL categories. Participants in category 4 were older than participants in the other categories (63 years v. 55-56 years, p=0.011) and were more likely to report being retired (62% v. 27%, p=0.002) (Table 3).

In comparison with the HealthIron study, which recruited a large representative sample of Australian adults with haemochromatosis, our cohort consisted of a lower percentage of males (41% v. 47%) and a higher rate of clinical penetrance (categories 3 and 4: 63% v. 24%) [8]. In addition the median age of HealthIron participants at follow-up by genotype ranged between 63.2 and 66.6years (no mean age reported), older than the median age of our cohort (57 years). Our study thus recruited a more severely affected population on average.

Table 3: Demographic characteristics

	diary completers (n=157)	diary non-completers (n=109)	p value
Mean age (range, SD)	56yrs (19-83, SD=13.16)	48yrs (18-73, SD=13.75)	p<0.001
Male	41.4% (65)	42.2% (46)	0.498
Employment status:			
employed full-time	29.3% (46)	30.6% (33)	0.466
employed part-time	14.0% (22)	15.7% (17)	0.413
retired	33.6% (46)	17.9% (12)	0.014
other	27.0% (43)	57.0% (62)	-
Category of haemochromatosis			
category 1	7.6% (12)	11.4% (10)	0.226
category 2	29.3% (46)	26.1% (23)	0.354
category 3	49.7% (78)	51.1% (45)	0.466
category 4	13.4% (21)	9.1% (8)	0.217

Diary completers (n=157)

	Category 1 (n=12)	Category 2 (n=46)	Category 3 (n=78)	Category 4 (n=21)
Mean age (range, SD)	56 (SD=7.9,41-69)	55 (SD=14.2,28-81)	55 (SD=13.8,19-83)	63 (SD=8.7,46-79)
Male	25% (3)	48% (22)	36% (28)	57% (12)
Employment status:				
employed full-time	8% (1)	30% (14)	37% (29)	10% (2)
employed part-time	33% (4)	17% (8)	13% (10)	0%
self-employed	17% (2)	11% (5)	8% (6)	14% (3)
retired	25% (3)	28% (13)	27% (21)	62% (13)
other	17% (2)	13% (6)	15% (12)	14% (3)

4.5.2 Base-case results

Mean and 95% confidence intervals for health sector, other sector and time-loss costs associated with the categories of (diagnosed) haemochromatosis are displayed in Table 4. A breakdown of these costs is displayed in Appendix 4C. The mean costs for each perspective increased as severity of disease increased. From the societal perspective, mean annual costs per patient in category 1 were AUD1,431 as compared to AUD11,882 in category 4. The main drivers of this increase were health sector and productivity costs. Similarly, mean costs from the government perspective increased from AUD824 for category 1 to AUD10,393 for category 4, with health sector and transfer costs being the main drivers. Mean costs from the patient perspective increased from AUD607 in category 1 to AUD2,066 in category 4. This increase was largely driven by health sector costs.

Table 4: Costs of haemochromatosis by category

	Patient perspective (AUD/person)		Government perspective (AUD/person)		Societal perspective (AUD/person)	
	mean cost (95%CI)	Median costs [IQR]	mean cost (95%CI)	Median costs [IQR]	mean cost 95%CI)	Median costs [IQR]
Category 1						
Health sector costs	560 (165-989)	197 [6-1201]	824 (278-1454)	552 [0-1440]	1384 (546-2308)	1498 [14-2138]
Other sector costs	47 (0-136)	0 [0-23]	n/a	n/a	47 (0-136)	47 [0-23]
Time-loss costs	n/a	n/a	0	0	0	0
TOTAL	**607 (209-1041)**	**250 [6-1314]**	**824 (287-1441)**	**552 [0-14404]**	**1431 (643-2262)**	**1559 [14-2212]**
Category 2						
Health sector costs	765 (497-1098)	341 [131-1129]	1949 (1162-3018)	899 [247-2305]	2722 (1761-3867)	1805 [488-3771]
Other sector costs	54 (32-80)	13 [0-93]	n/a	n/a	54 (32-80)	13 [0-93]
Time-loss costs	n/a	n/a	0	0	1517 (572-2852)	0 [0-1775]
TOTAL	**819 (544-1154)**	**463 [147-1244]**	**1949 (1162-3018)**	**8994 [247-2305]**	**4293 (2754-6110)**	**1993 [488-6391]**
Category 3						
Health sector costs	1464 (1197-1796)	1140 [611-2133]	2638 (2061-3287)	1978 [745-3558]	4126 (3336-5036)	3505 [1335-5174]
Other sector costs	94 (62-137)	34 [0-107]	n/a	n/a	94 (62-137)	34 [0-107]
Time-loss costs	n/a	n/a	1043 (239-2140)	0	5311 (3304-7837)	0 [0-5329]
TOTAL	**1558 (1268-1913)**	**1149 [425-2234]**	**3681 (2557-5109)**	**2064 [819-3640]**	**9531 (7169-12609)**	**5185 [2043-12523]**
Category 4						
Health sector costs	1904 (1078-2859)	1149 [28-2404]	4583 (2242-7861)	2519 [939-4816]	6518 (3576-10354)	3699 [1706-7691]
Other sector costs	162 (67-281)	41 [0-345]	n/a	n/a	162 (67-281)	41 [0-345]
Time-loss costs	n/a	n/a	5811 (1849-10169)	0	5202 (1086-10576)	0 [0-3526]
TOTAL	**2066 (1208-3028)**	**1432 [628-2872]**	**10393 (5172-16558)**	**4732 [996-20976]**	**11882 (5750-19707)**	**5410 [1891-14208]**
Asymptomatic (categories 1 & 2)						
Health sector costs	723 (480-1017)	327 [54-1129]	1716 (1125-2604)	844 [134-1941]	2445 (1719-3422)	1670 [191-2953]
Other sector costs	53 (30-79)	0	n/a	n/a	53 (30-79)	0 [0-76]
Time-loss costs	n/a	n/a	0	0	1203 (454-2269)	0
TOTAL	**775 (528-1078)**	**388 [54-1244]**	**1716 (1125-2604)**	**844 [134-1941]**	**3701 (2423-5296)**	**1960 [191-4471]**
Symptomatic (categories 3 & 4)						
Health sector costs	1557 (1289-1856)	1149 [613-2185]	3051 (2356-3937)	2130 [844-3620]	4633 (3752-5672)	3567 [1407-5528]
Other sector costs	109 (76-149)	34 [0-121]	n/a	n/a	109 (76-149)	34 [0-121]
Time-loss costs	n/a	n/a	2054 (1007-3231)	0	5288 (3313-7423)	0 [0-5160]
TOTAL	**1666 (1384-1996)**	**1163 [648-2440]**	**5105 (3853-6720)**	**2416 [864-4117]**	**10030 (7705-12670)**	**5294 [2033-12344]**

IQR: interquartile range

These groups were further analysed by comparing the mean costs for diagnosed asymptomatic haemochromatosis patients (categories 1 and 2) with diagnosed symptomatic patients (categories 3 and 4) (Table 4). From the societal perspective, the mean cost per symptomatic patient was almost three-fold higher than an asymptomatic patient (AUD3,701 and AUD10,030 respectively). Health sector costs accounted for 66% of costs for asymptomatic patients, whereas for symptomatic patients, 53% of costs were attributable to productivity losses and 46% to health sector costs.

From the government perspective, the mean annual cost per symptomatic patient was almost three times higher than for an asymptomatic patient (AUD1,716 v. AUD5,105). All costs for asymptomatic patients were attributable to health sector costs, whereas for symptomatic patients, 60% of costs were related to health sector costs and 40% to transfer payments.

From the patient perspective, the mean annual cost for a symptomatic patient was double that of an asymptomatic patient (AUD1,666 v. AUD775 respectively). For both groups, almost all costs were attributable to health sector costs (93% respectively), with just 7% respectively accounted for by other sector costs, i.e. transport.

4.5.3 Population cost estimates

To estimate costs associated with diagnosed haemochromatosis for Australia, these costs were extrapolated to the Australian population, adjusted for age and ancestry (Table 2). The overall cost attributable to diagnosed haemochromatosis from a societal perspective was AUD106 million, with 60% of this related to health sector costs and 39% to productivity losses (Table 5). At a penetrance of 13.9%, asymptomatic patients accounted for a higher proportion of total costs than symptomatic patients (AUD74million v. AUD32 million). The main driver of costs for asymptomatic patients were health sector costs (66%), whereas for symptomatic patients, both productivity losses (53%) and health sector costs (46%) were the main drivers.

From the government perspective, the total estimated costs of diagnosed haemochromatosis were AUD51 million. For asymptomatic patients, all costs were associated with health sector costs; for symptomatic patients, 60% were attributable to health sector costs and 40% to transfer payments. Across all diagnosed patients with haemochromatosis, health sector costs accounted for 87% of costs, with transfer payments, accounting for the balance.

From the patient perspective, the majority of costs for all patients arose from health sector costs (93%). Other sector costs, which consisted entirely of costs attributable to transport, were relatively minor (7%). At a penetrance of 13.9%, asymptomatic patients accounted for higher costs than symptomatic patients (AUD15 million v. AUD5 million).

Table 5: Estimated total costs (AUD) for the Australian population from patient, government and societal perspectives, based on 31% of HMZ being diagnosed

	Patient perspective	Government perspective	Societal perspective
Asymptomatic *(Categories 1 and 2)*			
Health sector costs	14,416,937	34,240,100	48,778,323
Other sector costs	1,049,088	0	1,049,088
Time-loss costs	0	0	24,004,356
TOTAL	**15,466,025**	**34,240,100**	**73,831,767**
Symptomatic *(CATEGORIES 3 and 4: 13.9% penetrance)*			
Health sector costs	5,014,126	9,825,201	14,921,578
Other sector costs	350,388	0	350,388
Time-loss costs	0	6,615,703	17,029,897
TOTAL	5,364,514	16,440,903	32,301,863
ALL *(based on 13.9% clinical penetrance)*			
Health sector costs	**19,431,063**	**44,065,300**	63,699,900.41
Other sector costs	**1,399,477**	**0**	1,399,476.62
Time-loss costs	**0**	**6,615,703**	41,034,252.90
TOTAL	**20,830,539**	**50,681,003**	**106,133,629.93**

As the costs reported in Table 5 only include 31% of C282Y homozygotes (i.e. those who are assumed to be diagnosed), costs were also calculated for the estimated 69% of undiagnosed homozygotes. Total combined costs were estimated to be AUD274 million, with the undiagnosed group accounting for 61% of this (Table 6). Health sector costs were estimated to be AUD137 million overall, and time-loss costs AUD132 million. For the undiagnosed

group, the total costs were estimated to be AUD168million, with asymptomatic patients accounting for almost two-thirds of this. Undiagnosed symptomatic patients were estimated to cost AUD58 million, with two-thirds of this attributed to time-loss costs. Due to the low penetrance estimate used, the asymptomatic group accounted for greater total costs than the symptomatic group (AUD183 million v. AUD91 million).

Table 6: Estimated total costs (AUD) for diagnosed and undiagnosed C282Y homozygotes in the Australian population from the societal perspective

	Diagnosed (31%)	Undiagnosed (69%)
Asymptomatic *(Categories 1 and 2)*		
Health sector costs	48,778,323	53,703,895
Other sector costs	1,049,088	2,335,068
Time-loss costs	24,004,356	53,429,050
SUB-TOTAL	**73,831,767**	**109,468,013**
TOTAL	**183,299,780**	
Symptomatic *(Categories 3 and 4)*		
Health sector costs	14,921,578	19,570,021
Other sector costs	350,388	779,896
Time-loss costs	17,029,897	37,905,254
SUB-OTAL	**32,301,863**	**58,255,172**
TOTAL	**90,557,035**	
ALL		
Health sector costs	63,699,900	73,273,916
Other sector costs	1,399,477	3,114,964
Time-loss costs	41,034,253	91,334,305
SUB-TOTAL	**106,133,630**	**167,723,185**
TOTAL	**273,856,815**	

As clinical penetrance has been shown to be higher in males than females [7, 8, 13, 14, 57], societal costs were also calculated based on sex (Table 7). These estimates were taken from Allen and colleagues' work (28.4% of males and 1.2% of female homozygotes) [8]. Overall, the total estimated cost for both diagnosed and undiagnosed C282Y homozygotes was AUD278 million. Males accounted for 60% of these costs. For diagnosed males, health sector costs were the main driver (AUD35 million), whereas for undiagnosed males, time-loss costs were the main contributor (AUD61 million). Female C282Y homozygotes (diagnosed and undiagnosed) were estimated to cost AUD110 million. Due to the low penetrance estimate

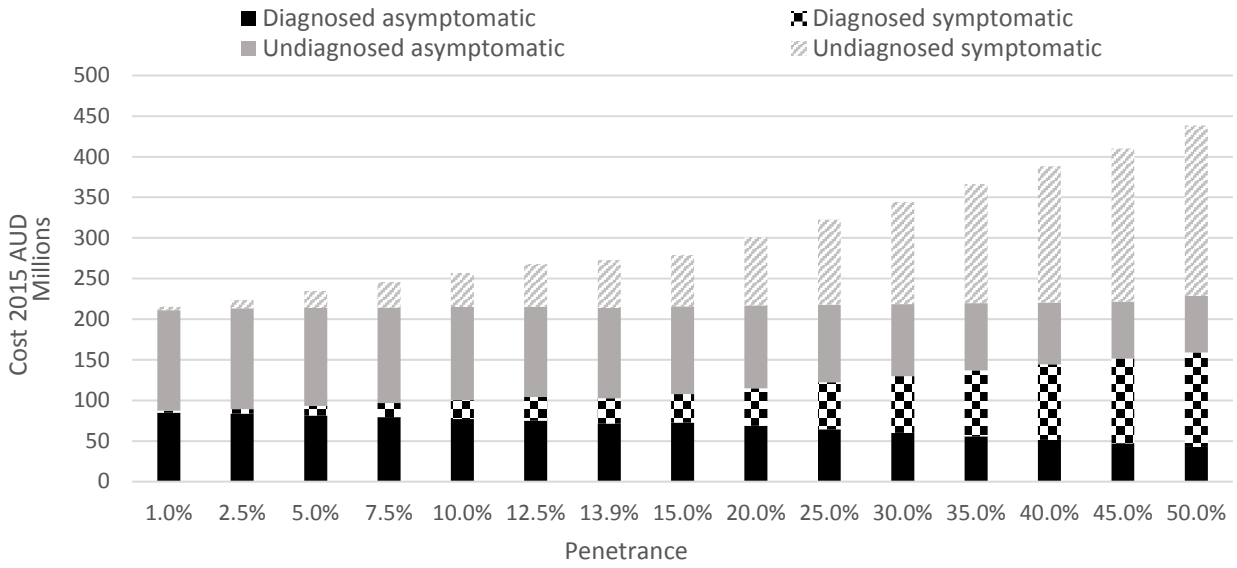
used (1.2%), symptomatic females accounted for a small proportion of costs (4%) in comparison with asymptomatic females.

Table 7: Estimated total costs (AUD) for the male and female Australian populations (societal perspective)

	Male *28.4% penetrance*		**Female** *1.2% penetrance*	
Asymptomatic *(Categories 1 and 2)*				
	Diagnosed	**Undiagnosed**	**Diagnosed**	**Undiagnosed**
Health sector costs	19,972,179	22,329,842	28,413,891	30,802,688
Other sector costs	429,547	970,911	611,015	1,339,749
Time-loss costs	9,828,532	22,215,563	13,982,792	30,654,995
TOTAL	**30,230,258**	**45,516,317**	**43,007,788**	**62,807,431**
Symptomatic *(CATEGORIES 3 and 4)*				
Health sector costs	15,010,910	19,992,369	653,930	844,749
Other sector costs	352,486	796,729	15,356	33,665
Time-loss costs	17,131,851	38,723,353	746,326	1,636,198
TOTAL	**32,495,246**	**59,512,478**	**1,415,611**	**2,514,612**
ALL				
Health sector costs	34,983,089	42,322,238	29,067,820	31,657,437
Other sector costs	782,033	1,767,639	626,461	1,373,413
Time-loss costs	26,960,383	60,938,917	14,729,118	32,291,193
TOTAL	**62,725,505**	**105,028,795**	**44,423,400**	**65,322,043**
Total for sexes	167,754,300		109,745,443	
Total costs combined	**277,499,743**			

The impact of penetrance estimates on costs was analysed by varying penetrance from 1% to 50% [8, 25, 26, 52, 53] (ceteris paribus) (Figure 1). This analysis showed that increased penetrance resulted in increased cost. At 1% penetrance, total costs were estimated to be AUD215 million; when penetrance was increased to 50%, total estimated costs increased to AUD459 million [7].

Figure 1: Sensitivity analysis of penetrance rate on estimated cost



4.6 Discussion

This cost of illness study, which includes health sector, other sector and time-loss costs, is the first to be published for hereditary haemochromatosis. Costs have been reported from the societal, government and patient perspectives using the most robust prevalence and penetrance estimates available for the Australian population. From the societal perspective the mean cost per diagnosed haemochromatosis patient was significantly lower for asymptomatic patients (AUD3,701) than for symptomatic patients (AUD10,303). However, due to the low penetrance rate used in the base case analysis (13.9%), the asymptomatic group accounted for the majority of costs at the population level.

From the societal perspective, the total estimated costs of haemochromatosis in Australia were AUD274 million in 2015, consisting of AUD137 million for health sector costs and AUD132 million for time-loss costs. This estimate was based on several assumptions from a robust Australian study [8] and included diagnosed and undiagnosed C282Y homozygotes. Whilst these assumptions add uncertainty to cost estimates, they were all based on the most robust data available to-date.

The sensitivity analysis of varying penetrance rates showed that lower penetrance likely leads to lower costs. As haemochromatosis is relatively straightforward to diagnose and treat, reducing clinical penetrance should be achievable. Early diagnosis could be accomplished through awareness raising campaigns targeting the public and/or medical practitioners, or through a population screening program. Whether these interventions are cost-effective or not is beyond the scope of this study. Importantly, reducing penetrance is likely to lead to improved health and quality of life amongst people with haemochromatosis. A recent study reported quality of life utility to be negatively correlated with the number of haemochromatosis-related symptoms [58]. It is likely that increasing the rate of early diagnosis and treatment is likely to improve haemochromatosis patients' utility.

There are several limitations to this study. First, use of a convenience sample may introduce bias, with possible questions of generalizability. To mitigate this, prevalence and penetrance estimates were taken from a robust Australian epidemiological study, and total costs were based on these data. Second, the small sample size resulted in large confidence intervals around the cost estimates. Lastly, several assumptions were adopted when extrapolating costs to the population level. Whilst this was unavoidable, increased uncertainty around the cost estimates resulted, although this was explored in sensitivity analysis. The results of this study should be viewed as indicative cost estimates. A strength of this study is the bottom-up approach to costing, which combines resource utilization data and unit costs at an individual level [59].

Whilst the costs associated with haemochromatosis in Australia are not as substantial as those reported for conditions such as psychosis (AUD4.9 billion in 2010) [38], multiple sclerosis (AUD1.04 billion in 2010) [37], and diabetes (AUD1.4 billion in 2008/09) [60], they are sizeable and incur an opportunity cost. Unlike these other disorders, symptomatic haemochromatosis could feasibly be substantially reduced by increasing early diagnosis. The cost data reported in this paper can be used to populate cost-effectiveness models of haemochromatosis to identify optimal screening and intervention strategies. Such

interventions would likely result in reduced opportunity costs related to haemochromatosis, and importantly, reduce the morbidity and mortality due to this condition.

4.7 References

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Health sector costs

Prescribed and non-prescribed medications, supplements

Mean annual cost per participant was calculated by summing all annual costs and applying the relevant safety net threshold. For pharmaceuticals, the Australian health system incorporates a safety net for all holders of the national health insurer Medicare card (all permanent citizens and holders of permanent residency visas are eligible). The maximum cost of medication listed on the Pharmaceutical Benefits Scheme (PBS) is AUD37.70 (as of January 1, 2015). Any cost above this is borne by the government. When a patient has reached the threshold of AUD1,453.90, all PBS prescription costs are capped at AUD6.10 for the patient, with the government paying the balance. Alternately, for holders of both a Medicare card and government-issued concession card, the maximum cost for all PBS-listed prescriptions is AUD6.10. When the threshold of AUD366.00 is reached, all PBS prescriptions are cost free to the patient with the government paying the balance.

Medical appointments, investigations and interventions

Similar to the PBS, the Australian health system incorporates a safety net for medical services for all holders of the Medicare card: the Medicare Benefits Scheme (MBS). In 2015, when a patient's expenditure on medical items reached AUD2,000 (excluding medications), Medicare paid 80% of all further costs under the MBS, and the patient paid the remaining 20%. In the case where a patient was also a holder of a government issued concession card, the MBS safety net of AUD638.40 applied. Thereafter, Medicare would pay 80% of any further costs and the patient 20%.

Time-loss

Presenteeism and absenteeism were costed using questions adapted from the World Health Organization Health and Work Performance Questionnaire [1]. Absenteeism was measured by asking participants who were employed at the time of the interview 'How many days in the last four weeks have you stayed away from work for more than half the day because of haemochromatosis related health problems?'. A mean number of days absent was calculated for each participant and multiplied by 12 to derive an annual figure. Mean weekly earnings

were taken from the Australian Bureau of Statistics for age and sex for 2013 [2]. These were adjusted for inflation using the Consumer Price Index (CPI) for June 2013 as the base year (102.8) and for March 2015 (106.8) [3]. Annual days absent were then costed using this wage data and reported in 2015 AUD.

Presenteeism was measured by asking participants 'How many days in the last four weeks did you go to work while suffering from such (HH) health problems?', and 'On these days, what percentage of the time were you as productive as usual?'. Participants were asked to mark a scale of 0 to 100 indicating their response. Presenteeism was calculated by dividing productivity (0-100 scale) by 100 and multiplying this by the number of days attended employment when unwell due to HH-related symptoms by. This figure was then subtracted from the number of days employment was attended when the participant was unwell. This provided the number of days lost to presenteeism per month. A mean number of days over the three monthly cost diaries was calculated and multiplied by 12 to derive an annual figure. Costs associated with this loss were calculated in the same was as described for absenteeism, using ABS wage data.

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Appendix 4C: Breakdown of per patient costs

Table 1: Mean and median costs per patient in 2015 AUD

	Patient perspective		Government perspective		Societal perspective	
	Mean cost (95%CI)	**Median cost (IQR)**	**Mean cost (95%CI)**	**Median cost (IQR)**	**Mean cost (95%CI)**	**Median cost (IQR)**
category 1 (n=12)						
Medications & supplements	24.62 (0-77.45)	0	7.75 (0-23.26)	0	32.38 (0-84.63)	0
Medical appointments, investigations, interventions	521.79 (169.82-951.56)	146.70 (0-1110.30)	816.71 (296.80-1434.13)	551.94 (0-1439.94)	1338.50 (574.92-2133.48)	1497.60 (0-1923.03)
Hospital admissions	0	0	0	0	0	0
Specialised equipment	13.48 (2.59-27.62)	0 (0-30.24)	-	-	13.49 (3.11-27.63)	0 (0-30.24)
Transport	46.76 (0.00-140.49)	0 (0-22.61)	-	-	46.76 (0.00-140.49)	0 (0-22.61)
Productivity: absenteeism	-	-	0	-	0	0
Productivity: presenteeism	-	-	-	-	0	0
Productivity: HH patients	-	-	-	-	0	0
Productivity: carers	-	-	-	-	0	0
Transfer payments: HH patients	-	-	0	0	-	-
Transfer payments: carers	-	-	0	0	-	-
TOTAL	**606.66 (228.50-1039.82)**	**250.37 (6.00-1314.48)**	**824.46 (303.27-1427.60)**	**551.94 (0-1439.94)**	**1431.12 (553.80-2374.63)**	**1559.04 (13.86-2211.71)**
category 2 (n=46)						
Medications & supplements	86.22 (39.05-152.93)	0 (0-120.37)	18.98 (2.52-45.01)	0	112.85 (51.40-186.53)	0 (0-150.24)
Medical appointments, investigations, interventions	558.35 (388.92-736.67)	267.00 (49.20-863.50)	1509.84 (1059.15-2033.35)	868.35 (172.95-1940.58)	2068.19 (1414.97-2727.69)	1224.30 (487.80-3017.94)
Hospital admissions	82.17 (0-263.72)	0	420.31 (0-1263.74)	0	502.49 (0-1338.88)	0
Specialised equipment	38.45 (6.42-85.66)	0	-	-	38.45 (6.42-85.66)	0
Transport	54.11 (32.05-77.74)	12.92 (0-92.76)	-	-	54.11 (32.05-77.74)	12.92 (0-92.76)
Productivity: absenteeism	-	-	-	-	216.66 (22.05-482.45)	0
Productivity: presenteeism	-	-	-	-	246.70 (8.78-562.82)	0
Productivity: carers	-	-	-	-	1053.86 (215.12-2403.56)	0
Transfer payments: HH patients	-	-	0	0	-	-
Transfer payments: carers	-	-	0	0	-	-
TOTAL	**819.30 (543.12-1170.52)**	**462.51 (146.72-1244.36)**	**1949.13 (1192.00-3042.93)**	**898.35 (247.20-2304.69)**	**4293.31 (2853.24-6198.65)**	**1993.18 (487.80-6391.47)**

Appendix 4C: Breakdown of per patient costs

category 3 (n=78)						
Medications & supplements	195.31 (145.55-249.36)	121.70 (0-310.20)	98.49 (49.90-158.80)	0 (0-20.88)	317.34 (230.04-404.68)	150.24 (0-471.122)
Medical appointments, investigations, interventions	990.83 (801.63-1190.36)	823.20 (164.85-1434.15)	2500.35 (2009.34-3092.18)	1892.04 (744.60-3511.20)	3491.18 (2837.18-4236.45)	2682.90 (0-4715.25)
Hospital admissions	96.92 (0-242.31)	0	39.58 (0-132.32)	0	136.51 (0-301.02)	0
Specialised equipment	180.51 (84.82-299.79)	0 (0-98.62)	-	-	180.51 (84.82-299.79)	0 (0-98.62)
Transport	94.41 (59.47-135.87)	34.45 (0-106.80)	-	-	94.41 (59.47-135.87)	34.45 (0-106.80)
Productivity: absenteeism	-	-		-	1155.51 (606.09-1772.85)	0 (0-1035.59)
Productivity: presenteeism	-	-	-	-	3212.08 (1638.09-5235.51)	0 (0-2139.45)
Productivity: carers	-	-	-	-	943.56 (91.76-2062.44)	0
Transfer payments: HH patients	-	-	1042.93 (242.11-2112.96)	0	-	-
Transfer payments: carers	-	-	0	0	-	-
TOTAL	**1557.99 (1268.27-1905.82)**	**1148.58 (642.35-2233.89)**	**3681.36 (2523.90-4962.16)**	**2064.30 (818.85-3639.56)**	**9531.10 (7060.49-12320.70)**	**5185.32 (2043.02-12523.09)**
category 4 (n=21)						
Medications & supplements	378.72 (211.16-582.62)	219.60 (51.07-473.25)	590.70 (94.91-1505.37)	57.60 (0-372.51)	1000.98 (378.82-1954.42)	443.52 (51.07-1042.59)
Medical appointments, investigations, interventions	1187.78 (632.28-1968.47)	798.36 (322.20-1117.48)	2623.80 (1711.11-3577.33)	2260 (939.00-4559.82)	3811.58 (2557.68-5162.23)	1391.40 (1057.92-5875.90)
Hospital admissions	0	0	1368.21 (0-3318.08)	0	1368.21 (0-3318.08)	0
Specialised equipment	337.26 (113.94-601.34)	51.03 (0-381.04)	-	-	337.25 (113.94-601.34)	51.03 (0-381.04)
Transport	162.28 (62.64-276.00)	41.34 (0-344.53)	-	-	162.28 (62.64-276.00)	41.34 (0-344.53)
Productivity: absenteeism	-	-	-	-	1132.21 (0-2456.89)	0
Productivity: presenteeism	-	-	-	-	2852.62 (0-6370.48)	0
Productivity: carers	-	-	-	-	1217.19 (0-3485.48)	0
Transfer payments: HH patients	-	-	3873.75 (884.23-7744.43)	0	-	-
Transfer payments: carers	-	-	1936.88 (0-5084.30)	0	-	-
TOTAL	**2066.03 (1219.70-3118.82)**	**1432.28 (628.15-2871.98)**	**10393.34 (5416.29-16751.23)**	**4731.80 (996.48-20976.20)**	**11882.32 (5336.46-19167.23)**	**5410.16 (1891.39-14208.27)**

Appendix 4C: Breakdown of per patient costs

Asymptomatic patients:						
Categories 1 and 2 (n=58)						
Medications & supplements	73.47 (31.98-128.49)	0 (0-68.96)	16.69 (1.90-36.26)	0	96.20 (46.36-158.33)	0 (0-112.15)
Medical appointments, investigations, interventions	550.79 (392.83-714.06)	202.80 (25.56-863.50)	1366.43 (976.10-1786.13)	843.60 (133.77-1853.85)	1917.22 (1441.69-2453.93)	1340.10 (173.03-2732.19)
Hospital admissions	65.17 (0-213.86)	0	333.35 (0-977.81)	0	398.52 (0-1046.38)	0
Specialised equipment	33.28 (7.78-73.23)	0	-	-	33.28 (7.78-73.23)	0
Transport	52.59 (30.86-77.72)	0 (0-76.23)	-	-	52.59 (30.86-77.72)	0 (0-76.23)
Productivity: absenteeism	-	-	-	-	171.84 (19.19-367.91)	0
Productivity: presenteeism	-	-	-	-	195.66 (5.67-464.91)	0
Productivity: carers	-	-	-	-	835.82 (159.23-1836.13)	0
Transfer payments: HH patients	-	-	0	0	-	-
Transfer payments: carers	-	-	0	0	-	-
TOTAL	**775.31 (533.62-1052.38)**	**387.59 (53.93-1244.36)**	**1716.44 (1061.19-2600.52)**	**843.60 (133.77-1940.58)**	**3701.13 (2378.10-5123.92)**	**1959.13 (190.51-4471.40)**
Symptomatic patients						
Categories 3 and 4 (n=99)						
Medications & supplements	234.22 (177.25-296.42)	150.24 (0-364.26)	202.90 (80.19-413.34)	0 (0-129.78)	462.65 (306.48-701.19)	183.58 (0-605.52)
Medical appointments, investigations, interventions	1032.61 (840.29-1243.22)	798.36 (171.60-1362.00)	2526.54 (2036.47-3029.61)	1956 (744.60-3591.36)	3559.15 (2938.20-4204.57)	2733.20 (1016.40-4827.60)
Hospital admissions	76.36 (0-198.95)	0	321.41 (0-794.45)	0	397.78 (63.02-887.20)	0
Specialised equipment	213.76 (119.18-315.61)	0 (0-132.29)	-	-	213.76 (119.18-315.61)	0 (0-132.29)
Transport	108.80 (71.65-149.43)	34.45 (0-120.58)	-	-	108.80 (71.65-149.43)	34.45 (0-120.58_
Productivity: absenteeism	-	-	-	-	1150.57 (686.17-1719.70)	0
Productivity: presenteeism	-	-	-	-	3135.83 (1669.35-4808.05)	0 (0-1137.73)
Productivity: carers	-	-	-	-	1001.60 (281.91-1921.94)	0
Transfer payments: HH patients	-	-	1643.41 (610.27-2873.06)	0	-	-
Transfer payments: carers		-	410.85 (0-1026.87)	0	-	-
TOTAL	**1665.75 (1355.78-008.67)**	**1163.14 (647.52-2439.91)**	**5105.11 (3611.80-6971.61)**	**2416.04 (864.00-4117.46)**	**8950.91 (6604.63-11599.97)**	**5294.02 (2033.38-12344.49)**

Haemochromatosis in Australia: A Cost of Illness study

Haemochromatosis Cost diary

Over the next three months, we would like you to record all the resources (goods and services) that you used in the treatment, care and/or support of your haemochromatosis related health problems, regardless of whether you paid for them or not. We will need to know the amount of each type of resource you used, and if at all possible, how much it cost. To record this information we request that you complete a Haemochromatosis Cost Diary at the end of each month over this three month period.

Please note: People with haemochromatosis come from all lifestyles and experience a range of health problems of varying severity. For some people, these problems may impact their financial and/or employment situations. This cost diary may therefore contain questions and items that currently do not, and perhaps never will, apply to you. Please read the various sections carefully and then complete these as best you can.

Please remember, only include cost for medications, treatments and services for health problems that are associated with your haemochromatosis

Date: _____/_____/ 20___

1a. Date of birth ___/___/_____

1b. Sex:

Male……..0

Female……..1

1c. What is your postcode? _____

MEDICATIONS

2a. Prompt question: Have you used any medications for haemochromatosis related health problems in the last 4 weeks?

Yes…….1

No…….0 *(skip to Non-prescription medications)*

2b. Please complete the table below, with regard to medications that have you have used in the last 4 weeks that are for your haemochromatosis related health problems (e.g. arthritis, diabetes, heart disease).

Name of medication	Please tick one		Strength (in mg, gm etc)	How many tablets do you usually take in a day?	Out of the last 30 days, how many days have you taken this medication?	Total paid by you *(please leave blank if you don't remember)*	Did you use a script for this medications?
	Regular	Periodic					
A							
Abisart (irbesartan)							
Accupril (quinapril)							
Aclin (sulindac							
Actos (Pioglitazone)							
Advil (ibuprofen)							**Y/N**
Aldactone (spironolactone)							
Amaryl (glimepiride)							
Amlo (amlodipine)							

Amlodipine							
Arthrexin (indomethacin)							
Arthrotec (diclofenac & misoprostol)							
Aspirin (e.g. Aspro)							
Atacand (candesartan)							
Atenolol							
Avandamet (metformin & rosiglitazone)							
Avapro (irbesartan)							
Aylide (glimepiride)							
B							
Barbloc (pindolol)							
Betaloc (metopolol)							
Bicor (bisoprolol)							
Bispro (bisoprolol)							
Bisoprolol							
Brufen (ibuprofen)							
Burinex (bumetanide)							
Byetta (exenatide)							
C							
Cadatin (amlodipine & atorvastatin)							
Captopril							

Capoten (captopril)							
Cartia (aspirin)							
Carvedilol							
Celebrex (celecoxib)							
Co-Diovan (valsartan & hydrochlorothiazide)							
Corbeton (oxprenolol)							
Cozavan (losartan)							
D							
Daonil (glibenclamide)							
Dapa-tabs (indapamide)							
Deralin (propranolol)							
Diabex (metformin)							
Diabex XR (metformin)							
Diaformin (metformin)							
Diaformin XR (metformin)							
Diamicron (gliclazide)							
Dicarz (carvedilol)							
Diclofenac							
Dilatrend (carvedilol)							
Dimirel (glimepiride)							
Diovan (valsartan)							
Dithiazide (hydrochlorothiazide)							
Dolapril (trandolapril)							
E							
Enalapril							
Exforge (valsartan & amlodipine)							

F							
Feldene (piroxicam)							
Formet (metformin)							
Fosinopril							
Frusemide							
G							
Galvumet (metformin & vildagliptin)							
Galvus (vildagliptin)							
Gliclazide							
Glimel (glibenclamide)							
Glimepiride							
Glucobete (metformin)							
Glucovance (metformin & glibenclamide)							
Glyade (gliclazide)							
Gopten (trandolapril)							
H							
Humalog (insulin lispro)							
Humulin (isophane insulin)							
Hydrene (hydrochlorothiazide & triamterene)							
Hygroton (chlorthalidone)							
Hypurin Isophane (isophane insulin)							
Hypurin Neutral (neutral insulin)							
I							
Ibuprofen							**Y/N**
Imflac (diclofenac)							**Y/N**
Indapamide							
Inderal (propranolol)							
Indocid (indomethacin)							
Insig (indapamide)							
Inspra (eplerenone)							

Inza (naproxen)							
Irbesartan							
J							
Janumet (metformin & sitagliptin)							
Januvia (sitagliptin)							
Juvicor (sitagliptin & simvastin)							
K							
Kaluril (amiloride)							
L							
Lantus (insulin glargine)							
Lasix (frusemide)							
Lisodur (lisinopril)							
Lisinopril							
Lopressor (metopolol)							
M							
Melizide (glipizide)							
Meloxibell (meloxicam)							
Meloxicam							
Metformin							
Metformin XR							
Metex XR (metformin)							
Metopolol							
Minidiab (glipizide)							
Mixtard (isophane insulin)							
Mobic (meloxicam)							
Mobilis (piroxicam)							
Monopril (fosinopril)							
N							
Naprosyn (Naproxen)							

Natrilix (indapamide)							
Nebilet (nebivolol)							
Nidem (gliclazide)							
Noten (atenolol)							
Novomix (insulin aspart)							
Nurofen (ibuprofen)							Y/N
Nurofen Plus (ibuprofen & codeine)							Y/N
O							
Olmetec Plus (olmesartan & hydrochlorothiazide)							
Onglyza (saxagliptin)							
Orudis (ketoprofen)							
Oruvail (ketoprofen)							
Oziclide (gliclazide)							
P							
Panadeine (paracetamol & codeine)							Y/N
Panadeine Forte (paracetamol & codeine)							
Paracetamol (e.g. Panadol, Panadol Osteo)							Y/N
Pioglitazone							
Piroxicam							
Presolol (labetalol)							
Prilace (ramipril)							
Protophane (isophane insulin)							
Q							
Quinapril							
R							
Rafen (ibuprofen)							Y/N
Ramipril							
Renitec (enalapril)							

S							
Sevikar (olmesartan & amlodipine)							
Spiractin (spironolactone)							
T							
Tranjenta (linagliptin)							
Tenormin (atenolol)							
Tensig (atenolol)							
Teveten (Eprosartan)							
Toprol-XL (metopolol)							
Toradol (ketorolac)							
Trandate (labetalol)							
Triace (ramipril)							
Trandolapril							
Tryzan (ramipril)							
Twynsta (telmisartan & amlodipine)							
U							
Uremide (frusemide)							
V							
Visken (pindolol)							
Volirop (carvedilol)							
Voltaren (diclofenac)							
Z							
Zestril (lisinopril)							
Other *(please specify)*							**Y/N**
Other *(please specify)*							**Y/N**
Other *(please specify)*							**Y/N**

SUPPLEMENTS/OTHER PREPARATIONS

3a. Prompt question: Have you used any supplements (including fish oil, vitamin supplements) or other medicinal preparations for your haemochromatosis related health problems in the last four weeks?

Yes……..1

No……..0 *(skip to Health Services)*

3b. Please complete the table below, for non-prescribed medications that you used for symptoms/effects of haemochromatosis (including, but not limited to, arthritis) in the last 4 weeks.

Name of non-prescription medication/ treatment	**Please tick one**		**Strength (in mg, mls, grams etc)**	**How many tablets do you usually take in a day?**	**Out of the last 30 days, how many days have you taken this medication?**	**Total paid by you** *(please leave blank if you don't remember)*
	Regular	**Periodic**				
Vitamin supplements						
Mineral supplements						
Fish oil/omega 3/krill oil/algae oil						
Other (please specify)						

GP, PRIVATE SPECIALISTS AND OTHER HEALTH PROVIDER VISITS

4a. Please complete the table below with regard to visits to GPs, private specialists and other health providers for haemochromatosis related health problems in the community in the last 4 weeks. (Please note, this does NOT include visits to an outpatients clinic)

	Number of visits	Average length of visit (minutes)	Total fee charged (If known) $	How much did you pay $	How much did you get back (e.g. reimbursed by Medicare or a private health fund) $
GP, local doctor					
Gastroenterologist					
Haematologist					
Rheumatologist					
Cardiologist					
Ophthalmologist					
Other medical specialist (please specify)					
Community nurse					
Physiotherapist					
Social worker					

Psychologist					
Dietician/nutritionist					
Optometrist					
Acupuncturist					
Naturopath					
Other (please specify)					
Other (please specify)					

MEDICAL PROCEDURES, TESTS & INVESTIGATIONS

5a. Please complete the table below with regard to medical tests/investigations/procedures that you have had for haemochromatosis related health problems in the last 4 weeks.

Health professional visits for your haemochromatosis related health problems	Number of visits	Average length of visit (minutes)	Total fee charged (If known) $	How much did you pay $	How much did you get back (e.g. reimbursed by Medicare or a private health fund)
Therapeutic venepuncture (i.e. blood taken to remove iron)					

In the last 4 weeks, where did you usually have blood taken:

Hospital outpatients (public hospital)……0

Hospital outpatients (private hospital)……..1

Red Cross……2

Pathology service……..3

GP/medical clinic……4

Community health centre……5

Other *(please specify)* ……6

5b. What is the total number of times you have had a blood test (for testing purposes) in the last 4 weeks *(i.e. this does not include therapeutic venepuncture)*? _____

5c. Please complete the table below with regard to medical tests/investigations/procedures that you have had for haemochromatosis related health problems in the last 4 weeks.

Medical tests for your haemochromatosis related health problems	**Number of tests**	**Total fee charged (If known) $**	**How much did you pay $**	**How much did you get back (e.g. reimbursed by Medicare or a private health fund) $**
Blood test: Iron studies				
Blood test: Liver function test				
Blood test: Full blood count				
Blood test: HbA1c (glycosylated haemoglobin)				
Blood test: lipids (triglyceride, cholesterols)				
Other blood tests: *please specify:*				
X-ray: *specify what sort, area of your body:*				
Liver biopsy				
Liver ultrasound				
Endoscopy				
ECG (electrocardiogram)				
Urine test				
Other (please specify)				

Appendix 4D: Cost and resource use diary

HOSPITAL ADMISSION/ATTENDANCES

6a. Prompt question: Have you attended hospital for health problems related to your haemochromatosis related health problems in the last 4 weeks, excluding outpatient visits for venepuncture?

Yes…….1

No…….0 *(skip to Specialised equipment)*

6b. Please complete the table below with regard to hospitalisation attendances for your haemochromatosis related health problems in the last 4 weeks.

Please DO NOT include outpatient visits for venepuncture.

1. Whether it was an outpatient, emergency department and/patient inpatient admission
2. The reason
3. The length of the stay. If you were an Outpatient, enter the length of stay as '0' (zero) days. If you can't remember, just write don't know in the box, however an approximate duration would be sufficient. PLEASE do not include outpatient visits for venepuncture.
4. The total cost of the stay, if known
5. Total cost per visit/admission (before reimbursement)
6. The total cost to you in dollars

Hospital visits for your haemochromatosis related health problems	Outpatient attendances (number)	Emergency department visits (number)	Admissions last 4 weeks (number)	Reason(s) for each admission	Total length of stay(s)(days)	Total cost per visit/admission (before reimbursement)	Total cost to you ($)
Public hospital							
Private hospital							
Other (please specify)							

Appendix 4D: Cost and resource use diary

SPECIALISED EQUIPMENT

7a Related to you haemochromatosis and related health problems over the last 5 years. As people with haemochromatosis have highly variable health problems, there is equipment in this list you may never need to use. We would like to know if you have purchased any of the following:

Special equipment for your haemochromatosis related health problems	**How many of this item have you purchased in the last 4 weeks**	**How long does this last you**	**Total cost to you (subtract any rebates, reimbursements)**	**Who paid the balance or remainder**
Blood glucose sticks				
Pen-needles and syringes				
Urine testing strips/tablets				
Other (please specify)				

7b. Related to you haemochromatosis and related health problems over the last 5 years. If you have purchased any assistive devices, we would like to know:

1. **The month or year the equipment was purchased**
2. **The total cost of the equipment, if known**
3. **The total cost to you, in dollars**
4. **Who paid for the balance or remainder (e.g. government, private health insurance, friend or family)**
5. **Expected life of the item in years**

Special equipment for your haemochromatosis related health problems	**Month or year purchased**	**Total cost of item**	**Total cost to you (subtract any rebates, reimbursements)**	**Who paid the balance or remainder**	**Expected life of item (years)**
Heat pack/s					
Walking stick					
Walking frame					
Shower chair/stool					
Bath grab rails					
Non-slip bath mat					
Assistive devices for the household (e.g. can opener specifically for hand arthritis)					
Other (please specify)					
Other (please specify)					

7c. Related to you haemochromatosis and related health problems over the last 5 years. If you have <u>hired</u> any assistive devices, we would like to know:

1. The month or year the equipment was hired
2. The total cost of the hiring this equipment
3. The total cost to you, in dollars
4. Who paid for the balance or remainder (e.g. government, private health insurance, friend or family)
5. Expected life of the item in years

Special equipment for your haemochromatosis related health problems	**Month or year hired**	**Cost of hire** *(please circle the frequency of this hire payment)* **$**		**Total cost to you (subtract any rebates, reimbursements)**	**Who paid the balance or remainder**	**Expected life of item (years)**
Walking stick			Weekly Monthly Annually			
Walking frame			Weekly Monthly Annually			
Shower chair/stool			Weekly Monthly Annually			
Bath grab rails			Weekly Monthly Annually			
Non-slip bath mat			Weekly Monthly Annually			
Assistive devices for the household (e.g. can opener specifically for hand arthritis)			Weekly Monthly Annually			
Other (please specify)			Weekly Monthly			

			Annually			
Other (please specify)			Weekly Monthly Annually			

COMMUNITY SERVICES

8a. Please complete the table below, with regard to community services that you have used because of your haemochromatosis related health problems in the last 4 weeks.

Community services for your haemochromatosis related health problems	**Number of visits**	**Average length of visit (minutes)**	**Total fee charged (If known) $**	**How much did you get back (e.g. reimbursed by Medicare or a private health fund) $**
Support groups (for haemochromatosis and for any of the related health conditions)				
Meals on Wheels				
Home and Community Care (HACC)				
Welfare organisation				
Housing organisation				
Other (please specify)				
Other (please specify)				

TRANSPORT

We would like to know if, in the last 4 weeks, you incurred any out-of-pocket costs for travel that was specifically for haemochromatosis and related health conditions (e.g. therapeutic venepuncture, Drs appointments, etc).

9a. In the last 4 weeks, did you use a car/motorbike for such purposes?

Yes……1

No……0 *(skip to Q9b)*

9ai. If yes: please estimate how many kilometres you travelled for this purpose/s _____kms

9aii. Please specify any parking costs incurred $_____

9b. In the last 4 weeks, did you incur any out-of-pocket costs for travel (that was specifically for haemochromatosis and related health conditions) from any of the following:

Public transport $_____

Taxi $_____

Patient transport service $_____

IMPACT ON EMPLOYMENT

10. Are you currently employed?

Yes……1

No……0 (*finished)*

10a. How many days in the <u>last 4 WEEKS</u> have you <u>stayed away from your work</u> for more than half the day because of haemochromatosis related health problems?

☐☐ days

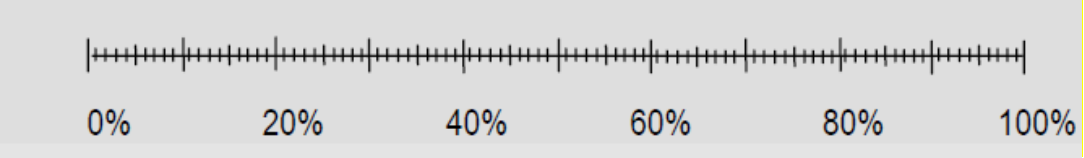
10b. How many days in the last 4 weeks did you <u>go to work while suffering from such health problems</u>?

☐☐ days

10c. On these days when you went to work suffering from health problems, what percentage of your time were you as productive as usual?

For example, if you were exactly as productive as usual please mark '100 %'.

Please indicate the percentage with a vertical line on the scale below.



10d. Did you take <u>paid</u> sick leave in the last 4 weeks for haemochromatosis related health problems?

No……..0

Yes……1

Not applicable…….2

10d1. If answered yes, how many days in the last 4 weeks have you taken sick leave?

_____ days

Chapter 5: Population screening for hereditary haemochromatosis in Australia: construction and validation of a state-transition cost-effectiveness model

5.1 Preface

In Chapters 3 and 4, the scope of the quality of life and economic impacts associated with haemochromatosis have been presented. These studies have provided evidence that the more severe stages of haemochromatosis are associated with higher costs and poorer quality of life. Chapters 5 and 6 are focused on evaluating screening interventions to identify the most cost-effective approach to reduce these burdens.

Chapter 5 presents a detailed overview of the construction and validation of a health economic model for screening for haemochromatosis. In order to validate the model and maximise model transparency, the International Society for Pharmacoeconomics and Outcomes Research guidelines for model transparency were followed. A state-transition Markov model was constructed and validated for Australian males aged 30 and females aged 45, both of northern European ancestry. The *status quo* approach to screening in Australia, (i.e. incidental and cascade screening) was used in the model simulation.

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de Graaff, B., Lei, S., Neil, A., Yee, K.C., Sanderson, K., Gurrin, L.C. & Palmer AJ. **"**Population screening for hereditary haemochromatosis in Australia: construction and validation of a state-transition cost-effectiveness model".

5.2 Abstract

Introduction: *HFE*-associated haemochromatosis, the most common monogenic disorder amongst populations of northern European ancestry, is characterised by iron-overload. Excess iron is stored in parenchymal tissues, leading to morbidity and mortality. Population screening programs are likely to improve early diagnosis, thereby decreasing associated disease. Our aim was to develop and validate a health economics model of screening using utilities and costs from a haemochromatosis cohort.

Methods: A state-transition model was developed with Markov states based on disease severity. Australian males (aged 30) and females (aged 45) of northern European ancestry were the target populations. The screening strategy was the *status quo* approach in Australia; the model was run over a lifetime horizon. Costs were estimated from the government perspective; costs and QALYs were discounted at 5% annually. Model validity was assessed using goodness-of-fit analyses. Second-order Monte Carlo simulation was used to account for uncertainty in multiple parameters.

Results: For validity, the model reproduced mortality, life expectancy (LE) and prevalence rates in line with published data. LE for C282Y homozygote males and females were 49.9 and 40.2 respectively, slightly lower than population rates. Mean (95%CI) QALYS were 15.7 (7.7-23.7) for males and 14.4 (6.7-22.1) for females. Mean discounted lifetime costs for C282Y homozygotes were AUD22,737 (3,670-75,793) for males and AUD13,840 (1,335-67,377) for females. Sensitivity analyses revealed discount rates and prevalence had the greatest impacts on outcomes.

Conclusion: We have developed a transparent, validated health economics model of C282Y homozygote haemochromatosis. The model will be useful to decision-makers to identify cost-effective screening strategies.

5.3 Introduction

HFE-associated hereditary haemochromatosis is the most common monogenic disorder amongst populations of northern European ancestry [1-3]. Whilst several mutations of the *HFE* gene have been identified, C282Y homozygotes account for between 80% and 90% of the burden of disease [4, 5]. The prevalence of this genotype has been estimated to be between 1 in 150, to 1 in 200 in populations of northern European ancestry [6-8]. Prevalence in populations of other ancestries is far lower, with estimates in the range of 1 in 1,000 for both Native and African Americans [9] and 1 in 1 million amongst Asian populations [10].

Clinically, haemochromatosis is characterised by iron overload, with excess iron stored in the parenchymal tissues of the liver, heart and pancreas [2, 11, 12]. Early symptoms of iron overload are non-specific, including fatigue, lethargy and arthropathy of the metacarpophalangeal joints. As iron overload progresses, liver disease, heart disease and type 2 diabetes can occur. Clinical penetrance is incomplete: a further genetic mutation is thought to play a role in this process [13, 14]. Whilst age of onset of iron overload varies, males typically develop overload at an earlier age, as menstruation assists in reducing iron stores in females [6].

Both diagnosis and treatment of haemochromatosis are straightforward. The former involves iron studies, most importantly transferrin saturation and ferritin, with confirmatory *HFE* genotyping. Treatment involves regular therapeutic venesection. When treatment is commenced prior to organ damage and maintained, the patient will not experience any long-term health problems related to haemochromatosis and retains normal life expectancy. However, as the early symptoms of haemochromatosis are non-specific, timely diagnosis is often missed until organ damage has occurred [15, 16]. In order to increase early diagnosis, population screening programs have been suggested [17-20].

Screening programs are typically resource intensive, therefore decision makers need to be confident that such interventions are likely to be cost-effective prior to their introduction. Economic modelling is a method that assists decision makers to evaluate the cost-effectiveness of a given intervention [21]. Long-term costs and consequences of the disorder with or without screening can be predicted by using existing clinical, epidemiological and cost

data combined in a suitable model. To date, no health economic model based on costs and utilities from a haemochromatosis cohort has been published. To address this lack of evidence, we have developed a model to assess screening strategies for the Australian setting for people homozygous for the C282Y mutation. The aim of this paper is to describe the construction and validation of our haemochromatosis screening model and to present model predictions for life expectancy, quality adjusted life years and total lifetime costs associated with haemochromatosis.

5.4 Methods

5.4.1 Model structure

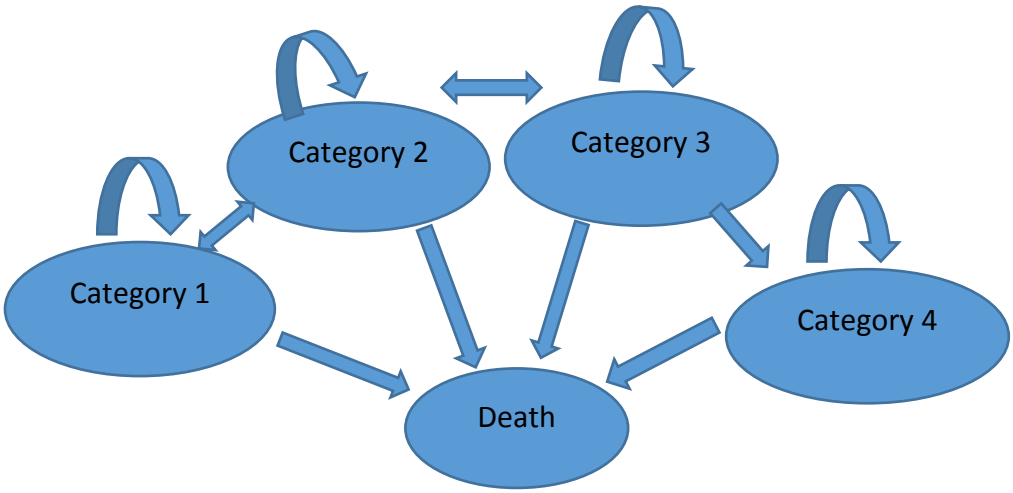
We constructed a cost-effectiveness model using a Markov approach allowing for modelling of multiple disease states over a lifetime horizon. The cycle length was one year, which continued to run until the death of all simulated subjects. A lifetime horizon was selected to reflect the chronic nature of haemochromatosis. The perspective taken was that of the government. This perspective was adopted as funding decisions are based, in part, on these government costs. Both costs and effectiveness were discounted by 5%, in line with the Australian guidelines [22]. The structure of the model is detailed in Appendix 5A. The model was constructed using TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts). Validation was conducted using TreeAge Pro and SPSS version 22.0.0.0. Modelled output data were exported into SPSS allowing for calculation of correlation coefficients and fitting linear curves for goodness-of-fit analyses.

Markov states were categorised according to the European Association for the Study of the Liver's (EASL) recommendations (Table 1) [17]. The four categories represent increasing severity of haemochromatosis and iron overload. For the Markov model, an absorbing 'Death' state was also included. Figure 1 provides an overview of the possible transitions between these states. Simulated participants could move between categories in either direction for all disease states except Category 4, as this included irreversible organ damage, and the absorbing state of 'Death'. The model was designed by an experienced clinician (KY) and health economists (AP, BdG, LS, AN).

Table 1: Categories of haemochromatosis [17]

Category 1	Genetic mutation only (C282Y homozygotes, H63D heterozygotes and compound heterozygotes)
Category 2	Genetic mutation and elevated iron studies, either transferrin saturation or serum iron
Category 3	Genetic mutation, elevated iron levels and early symptoms (e.g. arthritis, fatigue, lethargy)
Category 4	Genetic mutation, elevated iron levels and organ damage (e.g. liver cirrhosis, hepatocellular carcinoma, heart disease, Type 2 diabetes)

Figure 1: Structure of the Markov model. For C282Y homozygotes, simulated patients can move between the Markov states in the direction of the arrows



5.4.2 Base case populations

Two base-case populations were selected for analysis: males 30 years of age and females 45 years of age, both of northern European ancestry. The rationale for this decision was based on prevalence and penetrance estimates. Northern European ancestry was chosen as the prevalence of C282Y homozygosity is far higher than reported for populations of other ancestries [6, 9]. Amongst males, iron overload and related complications typically occur from the age of 30 onwards, and this has been the preferred age in other haemochromatosis models [23-25]. The second base-case population consisted of females 45 years of age, as

females tend to experience iron-overload following commencement of menopause [26].

5.4.3 Screening

The screening strategy was based on the *status quo* approach in Australia. Screening occurs either through a cascade approach, in which first degree relatives of a homozygote are offered genotyping and iron studies reimbursed by the Medical Benefits Scheme (MBS). Alternatively, screening occurs incidentally, consisting of a three step process: two consecutive elevated transferrin saturation (TfS) tests followed by *HFE* genotyping. In our model, when a participant tested negative to the genotype test, a referral to a specialist medical practitioner for further investigation was assumed (Appendix 5A). At present, this combined approach is estimated to diagnose 31% of C282Y homozygotes in Australia (L. Gurrin, Principal Investigator, HealthIron study, personal communication, March 16 2015).

5.4.4 Costs

Costs were reported from the government perspective, and were limited to direct medical costs, although other costs (indirect and direct non-medical costs) can also be included in the model. The costs were screening and state (Category) costs, both of which were reported in 2015 AUD (USD 0.75). Costs were deflated to constant prices using the price index for Government final consumption expenditure on hospitals and nursing homes, 2013/14 [27].

Direct medical costs associated with screening were sourced from the 2015 MBS [28]. The costs associated with haemochromatosis states were sourced from our previous cost of illness study [29]. This study estimated the costs of haemochromatosis on the basis of a national survey using a bottom-up approach. To date, these are the only published cost estimates for haemochromatosis. Costs were reported for each of the four EASL categories of haemochromatosis and are defined in Table 2. These costs were used for hypothetical participants who were diagnosed and received treatment. For participants either not diagnosed or not adhering to treatment, treatment costs, i.e. therapeutic venesection, were subtracted from the total costs for each category. Further, costs for undiagnosed Category 1 patients (either not screened or a false negative test) were set a zero. A brief description of the costing methodology is included here, but readers are directed to the original paper for a more detailed description.

Costs included were limited to resources funded by federal or state and territory governments. Pharmaceutical costs were based on the subsidy from the 2015 Pharmaceutical Benefits Scheme (PBS) Price Schedule of January 1, 2015 [30] – the difference between the dispensed price and the co-payment, if the dispensed price is greater. Unit costs for medical consultations and investigations (blood tests, liver biopsies, X-rays etc.) were derived from the MBS Book [28]. The National Hospital Cost Data Collection cost weights for Australian Refined Diagnosis-Related Group (AR-DRG) version 6.0x (2011-12) were used to estimate public hospital events [31]. Costs for public outpatient admissions were costed as reported by the Independent Hospital Pricing Authority [32].

Table 2: Key model parameters

Parameter		Base case		Range for SA		Distribution	Source
Prevalence of C282Y homozygotes[b]		0.0068		0.0044-0.0074		Triangular	[6, 8, 56, 57]
Probabilities for categories of haemochromatosis		Males	Females	Males	Females		
	Category 1	0.8	0.95	0.64-0.096[a]	0.76-1.00[a]	Triangular	[6, 58]
	Category 2	0.2	0.05	0.16-0.24[a]	0.04-0.06[a]	Triangular	
	Category 3	0	0	-	-	-	
	Category 4	0	0	-	-	-	
Annual transition probabilities:							
With treatment:							
	Category 1 to 2	0	0	-	-	-	
	Category 2 to 1	1-(mortality[#])	1-(mortality[#])	-	-	-	
	Category 2 to 3	0	0	-	-	-	
	Category 3 to 2	0.0083	0.0083	0.0064-0.0096[a]	0.0064-0.0096[a]	Triangular	
	Category 3 to 4	0	0	-	-	-	
	Category 4 to die	0.0167	0.0167	0.0134-0.0200[a]	0.0134-0.0200[a]	Triangular	[6, 59]
Without screening and/or treatment:						-	
	Category 1 to 2	0.071	0.0542	0.0568-0.0852[a]	0.04336-0.0650[a]	Triangular	
	Category 2 to 1	0	0	-	-	-	
	Category 2 to 3	0.0625	0.0167	0.050-0.075[a]	0.0134-0.0200[a]	Triangular	
	Category 3 to 4	0.0083	0.0083	0.0064-0.0096[a]	0.0064-0.0096[a]	Triangular	
	Category 4 to die	0.0167	0.0167	0.0134-0.0200[a]	0.0134-0.0200[a]	Triangular	
Adherence to therapeutic venesection (3-4 times annually)	Year 1	0.905		0.724-1.000[a]		Triangular	
	Year 2	0.837		0.670-1.000[a]		Triangular	
	Year 3	0.769		0.615-0.923[a]		Triangular	[51]
	Year 4	0.701		0.561-0.841[a]		Triangular	
	Year 5	0.633		0.506-0.760[a]		Triangular	
	Year 6	0.565		0.452-0.678[a]		Triangular	

Year 7	0.497	0.398-0.596 [a]	Triangular	
Year 8	0.429	0.343-0.515 [a]	Triangular	
Year 9	0.361	0.289-0.433 [a]	Triangular	
Year 10 and thereafter	0.293	0.234-0.352 [a]	Triangular	
Government costs incurred in categories of haemochromatosis*				
Category 1	824	434-1,213 [a]	LogNormal	
Category 2	1,949	1,162-3,018 [a]	LogNormal	[32]
Category 3	3,681	2,945-4,417 [a]	LogNormal	
Category 4	10,393	8,313-12,472 [a]	LogNormal	
Unit costs of screening strategies elements*				
GP Level A	16.95	n/a*	LogNormal	[29, 30]
GP Level B	37.05	n/a*	LogNormal	[29, 30]
Iron studies	27.70	n/a*	LogNormal	[29]
HFE genotype: blood	31.00	n/a*	LogNormal	[29]
Initial medical specialist appointment	72.75	n/a*	LogNormal	[29, 30]

	Males	Females	Males	Females		
Sensitivity:						
HFE genotype	0.92	0.92	0.736-1.00 [a]	0.736-1.00 [a]	Triangular	Genotype [60]; transferrin saturation [44]
First transferrin saturation	0.938	0.546	0.750-1.00 [a]	0.437-0.655 [a]	Triangular	
Second transferrin saturation	0.90	0.55	0.72-1.00 [a]	0.44-0.66 [a]	Triangular	
Specificity:						
HFE genotype	0.994	0.994	0.795-1.00 [a]	0.795-1.00 [a]	Triangular	
First transferrin saturation	0.981	0.981	0.785-1.00 [a]	0.785-1.00 [a]	Triangular	
Second transferrin saturation	0.996	0.994	0.797-1.00 [a]	0.795-1.00 [a]	Triangular	
Uptake of screening:						
Population [b]	0.05		0.025-0.075~		Triangular	Estimates[c]
Of these:						
Cascade screening	0.50		-		Triangular	
Incidental screening	0.50		-		Triangular	

Utilities		Male	Female	Male	Female	
	Category 1	0.88	0.71	0.70-1.00 [a]	0.57-0.85 [a]	Beta	[41]
	Category 2	0.85	0.77	0.68-1.00 [a]	0.62-0.92 [a]	Beta	[41]
	Category 3	0.59	0.60	0.47-0.71 [a]	0.48-0.72 [a]	Beta	[41]
	Category 4	0.59	0.41	0.47-0.71 [a]	0.33-0.49 [a]	Beta	[41]
Annual discount rate							
	Costs	0.05		0.00-0.07		-	[23]
	Effectiveness	0.05		0.00-0.07		-	

[*] All costs are in 2015 AUD; [a] One-way sensitivity analysis values ±20% of base-case value; [~] One-way sensitivity analysis values ±50% of base-case value; [b] This refers to persons of northern European ancestry; [c] These estimates were based on expert opinion as no data was available;[#] mortality rates used were age and sex specific, and obtained from the Australian Bureau of Statistics [47]; [*]Sensitivity analysis was carried out on total screening costs, not unit costs .
GP refers to general practitioner

5.4.5 Effectiveness

Health state utility values (HSUVs) were used to calculate quality adjusted life years (QALYs). Utility values were taken from a recently published study by our group, the only study date that has assessed utility values directly in people with haemochromatosis [33]. This study reported HSUVs amongst a sample of Australian adults with haemochromatosis, using the Assessment of Quality of Life 4D (AQOL-4D) instrument [33]. Mean utilities and their distributions were calculated for each of the four EASL categories (Tables 1 and 2).

5.4.6 Mortality

Mortality associated with haemochromatosis was assumed to be the same as the Australian population age and sex adjusted rates, with the exception of Category 4. Age and sex adjusted mortality was sourced from Australian life tables [34] (Table 2). For Category 4, as irreversible organ damage (e.g. liver cirrhosis, heart disease) characterises this category, an elevated probability of death was assigned to this state reflecting current literature. A multiplier of 2.45 (95%CI of 2.27 and 2.64) was applied to the age and sex-specific mortality rates for the Australian population, based on an estimate from an epidemiological study [35].

5.4.7 Bayes' revision

<u>Bayes' revision</u>

As with almost all diagnostic tests, the sensitivity and specificity of transferrin saturation and *HFE* genotyping as diagnostic tools for haemochromatosis are imperfect, that is, both less than 100%. To address this, the Bayes' revision function within the TreeAge model structure was used. This function, based on Bayes' theorem [36], combines prior and posterior probabilities (or, alternatively, combines a prior odds with a likelihood ratio to generate a posterior odds for a given hypothesis) as per the formula:

$$\mathrm{P(Hypothesis \mid Evidence)} = \frac{\mathrm{P(Evidence|Hypothesis)} \times \mathrm{P\ (Hypothesis)}}{\mathrm{P\ (Evidence)}}$$

Where P(Hypothesis) is the prior probability of the hypothesis of disease (usually taken to be the unadjusted population prevalence if we are considering a diagnostic test for a binary outcome) and P(Evidence) is the marginal probability of the evidence given that the

hypothesis is true, usually derived from a "sampling model" for the probability of the observed data given values of the sensitivity and specificity consistent with the hypothesis. The decision tree incorporated four posterior probabilities in both the incidental and cascade screening sub-branches, specific to the tests ordered. The estimates of sensitivity and specificity for genotyping [37] and transferrin saturation tests [38] are displayed in Table 2.

5.4.8 Sensitivity analyses

Probabilistic decision analysis with simultaneous sampling from distributions of key input parameters was used to address uncertainty. Tornado diagrams were produced for both populations to identify parameters with the greatest individual impact on costs and effectiveness. Prevalence of C282Y homozygosity, adherence to treatment, transition probabilities, Category 4 mortality rates, utility values and costs were varied by ±20% of the values used in the base-case analysis [39]. Screening uptake was varied by ±50% of the values used in the base-case analysis, reflecting the greater uncertainty given reliance on expert opinion. Discounting of both costs and effectiveness was varied between zero and 7%, from the base-case of 5%. Based on these results, one-way sensitivity analysis of all key input parameters was performed. For variables that were defined by a distribution, probabilistic sensitivity analysis was conducted to incorporate multiple parameter uncertainties simultaneously.

5.4.9 Model validity

Validation of the model followed the recommendations of the International Society of Pharmacoeconomics and Outcomes Research Task-Force 7 [40]. Face validity, internal validity and external validity were addressed. Face validity is a subjective approach involving people with clinical expertise in the disease area, thus ensuring the model incorporates the highest level of clinical evidence. The overall structure of the model, population, screening approaches, outcomes and assumptions were reviewed and validated by a hepatologist (KCY), biostatistician (LG) and four health economists (AP, LS, BdG, AN).

Internal validity involved assessments to ensure the correct mathematical calculations were implemented. This was conducted by validating equations and parameters against their sources (BdG, LS). Screening was modelled to predict mortality rates for males and females

at various ages. These estimates were compared with the mortality data that was used to populate the model [34]. One-way sensitivity analyses were conducted, as previously discussed, to ensure the results changed as expected when input parameter values were varied.

Assessing external validity involved comparing the predictions generated by our model with other published epidemiological and clinical data that were not used in our model. External validity was tested by estimating the life expectancy (LE) of 30 year old males and 45 year old females, and prevalence of C282Y homozygosity, and comparing to published data [34].

5.5 Results

5.5.1 Validity assessment

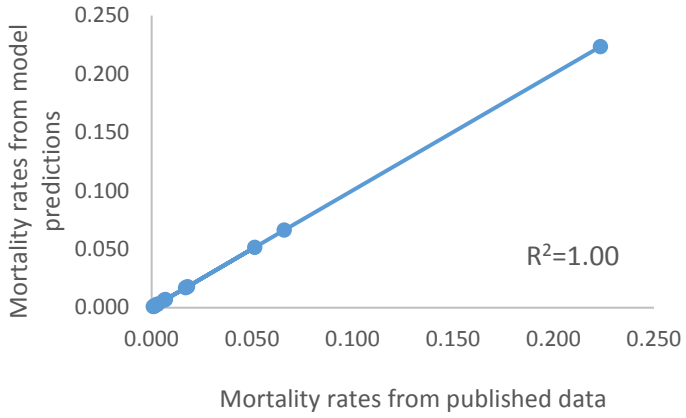
Face validity and internal validation

For face validity, the model structure was found to correctly represent all clinical aspects of haemochromatosis [7, 16, 41, 42]. To assess internal validity, mortality rates generated by the model were compared to the published rates used to build the model (Table 3) [34]. Specifically, the modelled predictions for mortality rates for males (at ages 30, 40, 50, 60, 70 and 80) and females (ages 45, 55, 65, 75 and 85) were plotted against the published rates and the goodness of fit for the linear relationship assessed (Figure 2). The correlation coefficient (R^2) was 1.00, indicating the model accurately reproduced the inputted mortality rates.

Table 3: Annual mortality rate for males and females from model predictions and inputs

Age (years)	Annual mortality rate from model predictions	Annual mortality rate from literature[47]
Males		
30	0.00079	0.00079
40	0.00134	0.00134
50	0.00291	0.00291
60	0.00678	0.00678
70	0.01690	0.01691
80	0.05126	0.05126
Females		
45	0.00121	0.00121
55	0.00270	0.00270
65	0.00626	0.00626
75	0.01783	0.01783
85	0.06603	0.06603

Figure 2: Goodness-of-fit test for model internal validation



External validity

For the overall hypothetical cohort, the model predicted a life expectancy (LE) of 30 year old males of 51.0 years, identical to the data reported in the ABS Life Tables (51.0 years) (Table 4) [34]. Similarly, for females aged 45, the model predicted life expectancy (LE) of 40.4 years, consistent with the data from the ABS Life Tables (40.4 years). These findings were as expected, given the relatively low prevalence of C282Y homozygotes. Further, the penetrance of Category 4 – the only state with elevated mortality rates – is very low, ranging between 0 and 0.01% (Figures 4 and 5). External validation analyses were also conducted for the prevalence of C282Y homozygosity (Table 4). Our model predicted a prevalence rate of 0.62%,

falling within the range established by two large, robust studies of 0.44% C282Y homozygosity for a population of 'white' North Americans and [43] and 0.75% for a Norwegian sample [38].

Table 4: External validity

Parameters	Model predictions	Data from literature
Life expectancy		
male aged 30	51.0	51.0 [47]
female aged 45	40.4	40.4 [47]
Prevalence of C282Y homozygotes amongst persons of northern European ancestry* (%):		
males	0.62 (0.0006)	0.75 [44]; 0.44 [50]
females	0.62 (0.0006)	

Note: * Whilst the prevalence of C282Y homozygosity is the same for both sexes, the model was run separately for males and females. As a result, they are reported separately.

To further assess external validity, the strength of the linear relationship between modelled LE and prevalence estimates with the respective published rates (Table 4) was assessed (Figure 3). The correlation coefficient (R^2) was 1.00, indicating the model accurately reproduced the published rates.

Figure 3: Goodness-of-fit test for model external validation

5.5.2 Model predictions

Table 5 displays the results of the base-case Monte Carlo simulations, calculated from age 30 years for males and 45 years for females. Life expectancy was estimated specifically for C282Y homozygotes: for 30-year old males, LE (standard deviation) was estimated to be 49.9 years (0.04), 1.1 years less than the Australian LE for 30 year old males (51.0 years). The projected LE for female C282Y homozygotes aged 45 was 40.2 years (0.01), 0.3 years less than the Australian LE for females of the same age (40.4 years). The mean (95% CI) discounted QALYs associated with screening were 15.7 (7.7-23.7) for males and 14.4 (6.7-22.1) for females. The model also predicted mean lifetime direct medical costs (95%CI) for male C282Y homozygotes as AUD22,737 (AUD3,670-85,793) and AUD13,840 (AUD1,335-67,377) for females.

Table 5: Results of base-case analyses

	Males (age 30 years) (SD)	Females (age 45 years) (SD)
Life expectancy (C282Y homozygotes)	49.9 (0.04)	40.2 (0.01)

	Population*		C282Y homozygotes	
	Costs (2015 AUD)	Effectiveness (QALYs)	Costs (2015 AUD)	LE (years)
Males				
Mean	145	15.654	22,737	49.91
Standard deviation	148	4.062	25,104	0.04
95% CI	29-498	7.694-23.668	3,670-85,793	-
Females				
Mean	91	14.390	13,840	40.15
Standard deviation	135	3.955	22,696	0.01
95% CI	15-414	6.660-22.142	1,335-67,377	-

Time (years) in disease states	C282Y homozygotes	
	Males (SD)	Females (SD)
Category 1	10.42 (0.00)	14.77 (0.00)
Category 2	13.53 (0.00)	19.54 (0.00)
Category 3	23.19 (0.00)	5.51 (0.00)
Category 4	2.79 (0.04)	0.41 (0.01)

* Population refers to the entire hypothetical cohort of males or females of northern European ancestry; 95% CI, 95% confidence interval

Time in states

The model projected the time spent in each disease state (Table 5). The low rates of uptake of screening and adherence to treatment were the drivers of transition to Categories 3 and 4: the states in which co-morbidities related to iron overload occur. Males spent a mean of 23years in Category 3 and three years in Category 4, whilst females, with lower clinical penetrance, spent a projected mean of six years in Category 3 and less than one year in Category 4.

The model predicted the probabilities of both the male and female cohorts being in each of the five Markov states for each stage of the model, until all hypothetical participants were in the absorbing Dead state (Figures 4 and 5). For both sexes, the probability of being in Category 1 increased between the first two stages, and conversely, the probability of being in Category 2 decreased. This result is a function of screening, in that 90.5% of Category 2 patients access treatment subsequent to screening. Therefore, most Category 2 participants transition to Category 1, the impacts of haemochromatosis being potentially reversible until Category 4. This effect is less dramatic for females as fewer females than males are in Category 2 at the time of screening (80% and 95% respectively).

For both sexes, the probability of being in Category 1 decreased over time reflecting reduced adherence to treatment; 90.5% in the first year to 29.3% in the tenth year and thereafter [44]. In turn, the probability of being in Categories 2, 3 or 4 increased. Participants in Category 4 had a higher probability of moving into the 'Death' state than other participants. In addition, the probability of transitioning into the 'Death' state increased with the advancing age of the cohort, in line with population data [34].

Figure 4: State probabilities for male C282Y homozygotes

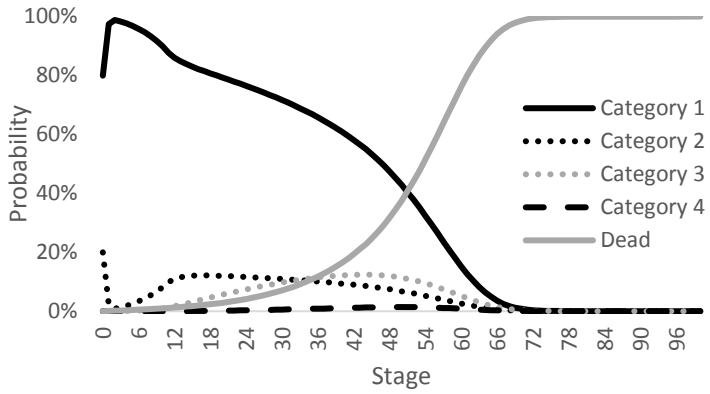
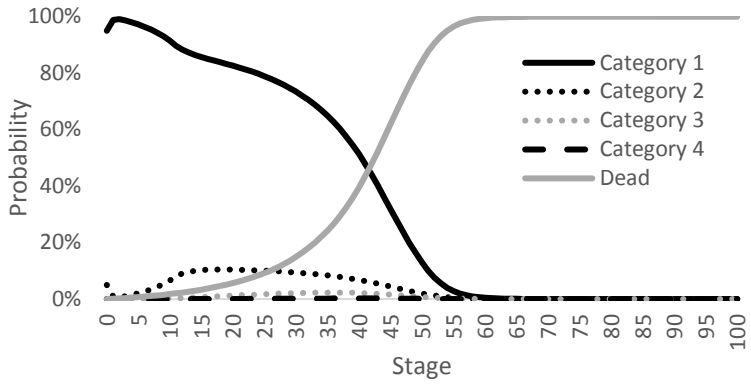


Figure 5: State probabilities for female C282Y homozygotes



5.5.3 Sensitivity analysis

One-way sensitivity analyses were carried out by varying the value by ±20% for all key parameters, with the exception of uptake of screening (±50%) and discounting (varied between 0 and 7%) (Appendix 5B). Tornado diagrams were constructed to identify parameters with the greatest effect on costs and effectiveness. The five parameters with the greatest impact (discount rate, prevalence, probability of starting in Category 1, transition from Category 1 to 2 and costs associated with Categories 2 and 3) are included in Appendix 5B.

For males, varying the discount rate had the most notable effect on both costs and effectiveness. With no discounting, mean costs increased from the base-case estimate of AUD145 to AUD497 and effectiveness increased from 15.7 to 42.2 QALYs. When the discount rate was set at 7%, mean costs decreased to AUD101 and effectiveness reduced to 11.9 QALYs. Varying the prevalence also had an impact on costs: increased the estimate by 20% increased mean costs to AUD185, and decreasing the estimated by 20% reduced costs to

AUD126. Varying uptake of screening (±50%) marginally impacted costs and effectiveness. Decreasing uptake reduced costs to AUD143, and increasing uptake increased costs to AUD146. No notable impact on effectiveness was observed (<0.001QALY). Varying the mortality multiplier had negligible effects on cost and effectiveness for males, (<AUD1 and <0.001 QALY respectively). For LE, varying the multiplier for mortality by ±20% (1.96 to 2.94) resulted in small changes. For males aged 30, from a base-case LE estimate of 40.1 years, decreasing the multiplier increased LE to 50.2years, and conversely, increasing the multiplier decreased LE to 49.7 years. One-way sensitivity analysis on other variables showed small impacts on costs and effectiveness (Appendix 5B).

For females, the parameter with the most effect on costs and effectiveness was the discount rate. Decreasing this to zero resulted in costs increasing to AUD264 from the base-case estimate of AUD91, and increasing this rate to 7% decreased costs to AUD64. Similarly, effectiveness increased from the base-case estimate of 14.4 to 33.1 QALY gained with no discounting and decreased to 11.3 QALY gained when the discount rate was set at 7%. Increasing the prevalence estimate increased costs to AUD114; when this was decreased, cost reduced to AUD79. Decreasing the uptake estimate by 50% reduced costs to AUD89, and increasing this estimate increased costs to AUD93. No notable change in effectiveness was observed (<0.001QALY). Similar to males, varying the mortality multiplier had negligible effects on costs and effectiveness (<AUD1 and <0.001 QALY gained respectively). The LE of females aged 45 increased by <0.01 years when the multiplier was decreased by 20% (40.2years), and conversely, LE decreased to 40.1 years when the multiplier was increased. All other sensitivity analyses revealed minor changes from the base-case estimate (Appendix 5B)

5.6 Discussion

This is the first economic model to be published using utility and cost data from a haemochromatosis cohort to populate a Markov model with probabilistic decision analysis: the approach best suited to this chronic, progressive disease. Just one other model has evaluated the cost-effectiveness of population screening for haemochromatosis, using a Markov model with probabilistic decision analysis. Our model has built on this previously published model by incorporating multiple disease states as recommended by the European

Association for the Study of the Liver, along with disease-specific cost and utility data derived from people living with haemochromatosis. Previous models used estimates of costs and utilities based on expert opinion.

The number of health technology assessments being conducted has increased over the past two decades and, with an increasing focus on value in health care, this is likely to continue. Whilst clinical studies are ideally placed to assess the short- to medium-term costs and effectiveness of interventions, long-term costs and effectiveness are most feasibly and efficiently assessed through modelling. Important considerations for modelling studies include use of the highest quality clinical and epidemiological data available, transparency, and acceptability to patient groups, expert clinicians, decision makers and healthcare payers. The model for haemochromatosis that we have constructed has aimed to address all of these issues.

The model was assessed for internal and external validity, returning correlation coefficients of 1.00 for goodness-of-fit analyses. These findings provide a level of confidence that the model correctly reproduces published data. All key input parameters, results of one-way sensitivity analyses and the structure of the model have been provided to enhance transparency.

The base-case analyses estimated the mean direct medical costs associated with screening and consequential treatment for those identified was AUD145 for males and AUD91 for females. The higher costs incurred by males than females are expected given the higher rate of clinical penetrance for males. One-way sensitivity analysis identified no parameters which altered this. Increasing the penetrance for females by increasing the probability of commencing in Category 2 (rather than Category 1) had a negligible effect on costs and effectiveness in comparison to the base-case results. Another factor contributing to the lower costs for females is the low sensitivity of transferrin saturation as a screening test for females. This results in missed diagnoses and lower total screening costs (two consecutive elevated transferrin saturation tests followed by confirmatory genotype), as fewer females than males will go on to have the second transferrin saturation test and genotype. In turn, potential venesection treatment costs are not accrued. Whilst in our model female C282Y homozygotes

who are not diagnosed, and therefore not receiving treatment, still accrue costs (with the exception of Category 1), these costs are smaller as venesection costs are excluded. Further, treatment costs accrue in the future, and are thus subject to discounting. Overall, the trade-off for this lower cost screening strategy is the reduced identification of female homozygotes. The trade-off between any cost savings versus the greater burden of disease generated is an issue which requires careful consideration.

Our model, consistent with other published studies, reported relatively high levels of uncertainty as evidenced by large standard deviations and 95%CI reported in the base-case analyses [4, 23, 45-47]. However, these uncertainties were addressed in our one-way sensitivity analyses and, with the exception of discounting, were found to have little impact on the base-case results. Our primary avenue to minimise uncertainty was by utilising patient derived information on costs and utilities associated with EASL categorisations.

Projected life expectancy for C282Y homozygotes was marginally lower than for the general population. The mortality multiplier applied to Category 4 of 2.45 [35], was in-line with other recent epidemiological work on mortality associated with haemochromatosis [48]. Whilst higher mortality rates were adopted for Category 4, the low penetrance rate for this category resulted in marginal impacts on overall mortality in both the base-case and sensitivity analyses.

Our model has been developed to allow for comparisons between the *status quo* approach of screening for haemochromatosis and alternatives, such as population level genetic or neonatal screening. In our accompanying paper in this issue, we report on an expansion of this model to compare several screening strategies for both adults and neonates and the assessment of the comparative cost-effectiveness [49]. Our model is well placed to assist decision makers in Australia to assess different screening strategies for haemochromatosis. Further, it is flexible enough that alternative parameters may be used to allow for cost-effectiveness analyses in different jurisdictions.

A transparent and validated health economics model of screening for C282Y homozygote haemochromatosis based on Australian economic, epidemiological and clinical data has been developed. The model will be useful to decision makers to identify cost-effective screening

and treatment strategies for C282Y homozygote haemochromatosis.

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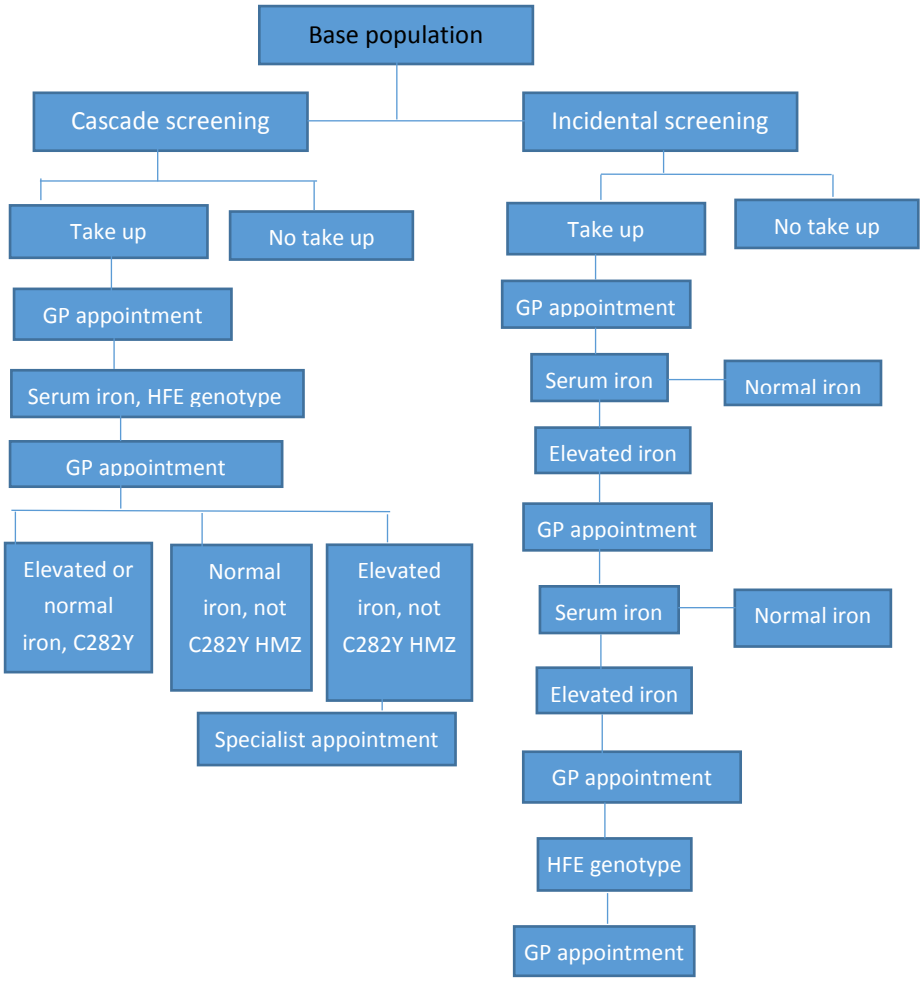
Appendix 5A: Screening flowchart



One-way sensitivity analyses: males and females

Parameters	Government perspective	
	Costs [a]	Effectiveness [b]
Males		
Discount rate: 0%	497	42.246
Discount rate: 7%	101	11.903
Prevalence: -20%	126	15.453
Prevalence: +20%	185	15.451
Probability of starting in category 1: -20%	158	15.451
Probability of starting in category 1: +20%	127	15.454
Transition from category 1 to 2~: -20%	133	15.453
Transition from category 1 to 2~: +20%	151	15.453
Costs: category 3(no treatment): -20%*	129	15.453
Costs: category 3(no treatment): +20%*	156	15.453
Parameters	Government perspective	
	Costs [a]	Effectiveness [b]
Females		
Discount rate: 0%	264	33.124
Discount rate: 7%	64	11.286
Prevalence: -20%	79	14.281
Prevalence: +20%	114	14.277
Costs: category 2(no treatment): -20%	76	14.280
Costs: category 2(no treatment): +20%	101	14.280
Probability of starting in category 1: -20%	107	14.280
Probability of starting in category 1: +20%	84	14.280
Transition from category 1 to 2~: -20%	79	14.280
Transition from category 1 to 2~: +20%	97	14.280

* At time of diagnosis, in the base-case this is assumed to be 0; [a] costs are lifetime costs reported in 2015 AUD; [b] effectiveness is presented in quality adjusted life years (QALYs)

Chapter 6: Cost-effectiveness of different population screening strategies for hereditary haemochromatosis in Australia

6.1 Preface

Chapter 3 and 4 presented evidence of the quality of life and economic impacts associated with haemochromatosis. Chapter 5 was concerned with presenting the construction and validation of a cost-effectiveness model for haemochromatosis. In Chapter 6, the application of the haemochromatosis health economics model is presented.

Four screening strategies were modelled: *HFE* genotyping using a blood sample, *HFE* genotyping with a buccal cell sample, sequential screening with two consecutive iron studies and confirmatory *HFE* genotyping, and the *status quo* was included as the comparator. The target populations for all strategies were males aged 30 years and females aged 45 years, both of northern European ancestry. In addition, *HFE* genotyping of neonates using Guthrie cards, irrespective of ancestry, was modelled, again using the *status quo* as the comparator.

From the government perspective, genotyping with a blood sample was the most cost-effective strategy for adult males; for adult females, the sequential approach was considered to be the most cost-effective. For male and female neonates, screening dominated the *status quo*. The results of this model can be used by decision-makers when considering resource allocation in relation to haemochromatosis screening interventions.

This chapter has been submitted to *Applied Health Economics and Health Policy*.

de Graaff, B., Neil, A., Lei, S., Yee, K.C., Sanderson, K., Gurrin, L.C. & Palmer AJ. "Cost-effectiveness of different population screening strategies for hereditary haemochromatosis in Australia".

6.2 Abstract

Introduction: Amongst populations of northern European ancestry, *HFE*-associated haemochromatosis is a common genetic disorder characterised by iron overload. In the absence of treatment, excess iron is stored in parenchymal tissues, causing morbidity and mortality. Population screening programs may increase early diagnosis and reduce associated disease. No contemporary health economic evaluation has been published for Australia.

Methods: A Markov model using probabilistic decision analysis was developed comparing four adult screening strategies: the *status quo* (cascade and incidental screening), genotyping with blood and buccal samples and transferrin saturation followed by genotyping (TfS); and two neonatal strategies: genetic screening and the *status quo*. Target populations were males (30 years) and females (45 years) of northern European ancestry, and neonates irrespective of ancestry. Cost-effectiveness was estimated from the government perspective over a lifetime horizon.

Results: All strategies for adult males were cost-effective compared to the *status quo*. The incremental costs (standard deviation) associated with genotyping (blood) were AUD7 (56), TfS AUD15 (45) and genotyping (buccal) AUD63 (56), producing ICERs of AUD1,673; 4,103; and 15,233/QALY gained respectively. For females, only the TfS strategy was cost-effective, producing an ICER of AUD10,195/QALY gained. Neonatal screening dominated the *status quo* for both sexes. Approximately 3% of C282Y homozygotes were estimated to be identified with the *status quo* approach, compared with 40% and 92% for adult and neonatal strategies respectively.

Conclusion: This model estimated that genotyping and TfS strategies are likely to be more cost-effective screening strategies than the *status quo*.

6.3 Introduction

HFE-associated hereditary haemochromatosis is the most common single-gene autosomal recessive disorder among populations of northern European ancestry [1-3]. People homozygous for the C282Y mutation in the *HFE* gene account for between 80% and 90% of clinical cases of iron overload [4, 5]. The prevalence of this genotype has been estimated from

population studies to be between 1 in 150 and 1 in 200 in populations of northern European ancestry [6-8]. Haemochromatosis is characterised by iron overload; treatment involves regular therapeutic venesection. Clinical penetrance is incomplete: a further genetic mutation is thought to play a role in this process [9, 10]. When treatment is delayed, morbidity and mortality can occur [2, 11, 12]. As diagnosis is often delayed until organ damage has occurred, population screening programs have been suggested to increase early diagnosis [13-18].

Modelled cost-effectiveness studies provide a pragmatic approach to assess the costs and effectiveness associated with various interventions in chronic diseases [19]. A clinical trial of population-based screening for haemochromatosis is unlikely, due to the high costs and long follow-up period required to comprehensively capture outcomes. Several studies have been published on the cost-effectiveness of screening for haemochromatosis, however a recent systematic review identified methodological issues with many of these, limiting their robustness and generalisability [20]. Assumptions regarding rates of prevalence, penetrance, screening uptake, adherence to treatment and utility values were highly variable, reflecting a paucity of data from high quality epidemiological and clinical studies at the time they were conducted. Most studies of screening interventions used cost/case detected or cost/life year gained (LYG) as outcome measures. Long-term outcomes for haemochromatosis – which have substantial effects on quality of life – may be better measured using quality adjusted life years (QALYs) [21, 22]. To date, just four cost-effectiveness studies reporting QALYs have been published [5, 23-25]. For the most part, the utility values used to calculate QALYs were notably higher than reported for relevant population norms [26], disease-specific utilities for comparable comorbidities [27-29] and for a recently reported cohort of people with haemochromatosis [22]. Use of elevated utility values may contribute to underestimates of QALY gains. The aim of this study was to assess the cost-effectiveness of adult and neonatal screening strategies for the Australian setting to identify people homozygous for the C282Y mutation, using the most robust clinical, epidemiological and health economic data available.

6.4 Methods

6.4.1 Model structure

We constructed a cost-effectiveness model that has been described in detail in our accompanying paper in this issue [30]. A brief description is provided here. A state-transition model utilising a Markov approach over a lifetime horizon was developed, with four Markov states based on disease severity along with the absorbing state 'Death' (Figure 1) [31].

Markov states were based on disease categories as recommended by the European Association for the Study of the Liver (EASL) (Table 1) [31]. At the time of diagnosis, it was assumed that no participants were in Categories 3 or 4; the probability of being in Categories 1 and 2 were 0.8 and 0.2 respectively for males, and 0.95 and 0.05 respectively for females. State transition probabilities were taken from a large Australian epidemiological study, and were dependent upon adherence to treatment (i.e. non-adherence resulted in a higher probability of transition to the next category of disease [6, 32, 33] (Table 2).

Figure 1: Structure of the Markov model. For C282Y homozygotes, simulated patients can move between the Markov states in the direction of the arrows. 'Categories 1,2 3 and 4' are temporary states and 'Death' is an absorbing state.

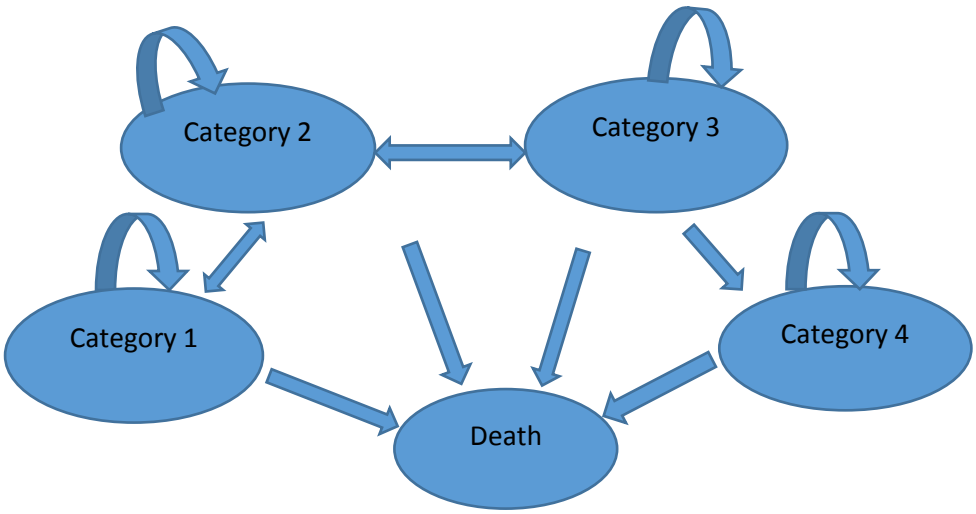


Table 1: Categories of haemochromatosis [25]

Category 1	Genetic mutation only (C282Y homozygotes, H63D heterozygotes and compound heterozygotes)
Category 2	Genetic mutation and elevated iron studies, either transferrin saturation or serum iron
Category 3	Genetic mutation, elevated iron levels and early symptoms (e.g. arthritis, fatigue, lethargy)
Category 4	Genetic mutation, elevated iron levels and organ damage (e.g. liver cirrhosis, hepatocellular carcinoma, heart disease, Type 2 diabetes)

Age and sex adjusted mortality was sourced from Australian life tables [34] (Table 2). Mortality for disease states was assumed to be the same as the Australian population age and sex adjusted rates with the exception of Category 4. As irreversible organ damage (e.g. liver cirrhosis, heart disease) characterises this category, a multiplier of 2.45 (95%CI 2.27-2.64) was applied to age and sex specific mortality based on recently published mortality estimates [35, 36].

Second order Monte Carlo simulation (probabilistic sensitivity analysis) was conducted by simultaneously sampling from multiple distributions around key inputs to address parameter uncertainty. When defining the distributions of model parameters, where insufficient data from the literature was available, triangular distributions were adopted. The model was constructed using TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts).

6.4.2 Base case populations

Adults

Two base-case populations were selected: 30 year old males and 45 year old females, both of northern European ancestry. The sex-specific ages were selected as they reflect typical ages for iron-overload to commence [23, 37, 38], and northern European ancestry as the prevalence of C282Y homozygosity is notably higher amongst this group than for populations of other ancestries [6, 39].

Neonates

Two base-case populations of male and female neonates irrespective of ancestry were also selected. This strategy reflects the existence of universal neonatal genetic screening in Australia, therefore avoiding additional infrastructure requirements.

Table 2: Key model parameters

Parameter	Base case		Range for SA		Distribution	Source
Prevalence of C282Y homozygotes						
Of northern European ancestry	0.0068		0.0044-0.0074		Triangular	[2-4]
Australian population	0.0039		0.00312-0.00468		Triangular	[5]
Probabilities for categories of haemochromatosis	Males	Females	Males	Females		[6]
Category 1	0.8	0.95	0.64-0.096[a]	0.76-1.00 [a]		
Category 2	0.2	0.05	0.16-0.24 [a]	0.04-0.06 [a]	Triangular	
Category 3	0	0	-		Triangular	
Category 4	0	0	-		-	
					-	
Annual transition probabilities:						
with treatment:						
Category 1 to 2	0	0	-	-	-	[6, 7]
Category 2 to 1	1-(mortality[#])	1-(mortality[#])	-	-	-	
Category 2 to 3	0	0	-	-	-	
Category 3 to 2	0.0083	0.0083	0.0064-0.0096[a]	0.0064-0.0096[a]	Triangular	
Category 3 to 4	0	0	-	-	-	
Category 4 to die	0.0167	0.0167	0.0134-0.0200[a]	0.0134-0.0200[a]	Triangular	
without screening and/or treatment:					-	
Category 1 to 2	0.071	0.0542	0.0568-0.0852[a]	0.04336-0.0650[a]	Triangular	
Category 2 to 1	0	0	-	-	-	
Category 2 to 3	0.0625	0.0167	0.050-0.075 [a]	0.0134-0.0200[a]	Triangular	
Category 3 to 4	0.0083	0.0083	0.0064-0.0096 [a]	0.0064-0.0096[a]	Triangular	
Category 4 to die	0.0167	0.0167	0.0134-0.0200 [a]	0.0134-0.0200[a]	Triangular	
Category 4 mortality multiplier [b]	2.45	2.45	1.96-2.94 [a]	1.96-2.94 [a]	Triangular	[8]
Adherence to therapeutic venesection (3-4 times annually)						
Year 1	0.905		0.724-1.000 [a]		Triangular	

Year 2	0.837	0.670-1.000 [a]	Triangular	
Year 3	0.769	0.615-0.923 [a]	Triangular	
Year 4	0.701	0.561-0.841 [a]	Triangular	[9]
Year 5	0.633	0.506-0.760 [a]	Triangular	
Year 6	0.565	0.452-0.678 [a]	Triangular	
Year 7	0.497	0.398-0.596 [a]	Triangular	
Year 8	0.429	0.343-0.515 [a]	Triangular	
Year 9	0.361	0.289-0.433 [a]	Triangular	
Year 10 and thereafter	0.293	0.234-0.352 [a]	Triangular	
Costs incurred in categories of haemochromatosis [*]				
Category 1	824	434-1,213 [a]	LogNormal	[10]
Category 2	1,949	1,162-3,018 [a]	LogNormal	[10]
Category 3	3,681	2,945-4,417 [a]	LogNormal	[10]
Category 4	10,393	8,313-12,472 [a]	LogNormal	[10]
Unit costs of screening strategies elements [*]				
GP Level A [c]	16.95	-	-	[11, 12]
GP Level B [c]	37.05	-	-	[11, 12]
Iron studies [c]	27.70	-	-	[11]
Genotype: blood [c]	31.00	-	-	[11]
Genotype: buccal [c]	150	-	-	Estimate [d]
Initial medical specialist consultation [c]	72.75	-	-	[11, 12]
Information pamphlet [c]	0.38	-	-	Estimate [e]
Neonatal heel prick screen [c]	0.88	-	-	[13]

Sensitivity:	Males	Females	Males	Females		
First genotype test	0.92	0.92	0.74-1.00 [a]	0.74-1.00 [a]	Triangular	Genotype [14]; TfS [15]
First transferrin saturation	0.938	0.546	0.75-1.00 [a]	0.44-0.66 [a]	Triangular	
Second transferrin saturation	0.90	0.55	0.72-1.00 [a]	0.44-0.66 [a]	Triangular	
Specificity:						
First genotype test	0.994	0.994	0.80-1.00 [a]	0.80-1.00 [a]	Triangular	
First transferrin saturation	0.981	0.981	0.78-1.00 [a]	0.78-1.00 [a]	Triangular	
Second transferrin saturation	0.996	0.994	0.80-1.00 [a]	0.80-1.00 [a]	Triangular	
Uptake of screening:						
Status quo		0.05		0.025-0.075~	Triangular	Estimate [d]
Of these: Cascade screening		0.50		-	Triangular	[16, 17]
Incidental screening		0.50		-	Triangular	[16, 17]
Genotype		0.469		0.23-0.70~	Triangular	[16, 17]
Neonatal heelprick		1.00		-	Triangular	[13, 18, 19]
Adult state iron studies		0.50		0.025-0.075~	Triangular	Estimate [d]
Utilities	Male	Female	Male	Female		
Category 1	0.88	0.71	0.70-1.00	0.57-0.85	Beta	[20]
Category 2	0.85	0.77	0.68-1.00	0.62-0.92	Beta	[20]
Category 3	0.59	0.60	0.47-0.71	0.48-0.72	Beta	[20]
Category 4	0.59	0.41	0.47-0.71	0.33-0.49	Beta	[20]
Annual discount rate						
Costs		0.05			-	
Effectiveness		0.05		0.00-0.07	-	[21]

* All costs are in 2015 AUD; [a] One-way sensitivity analysis values ±20% of base-case value; ~ One-way sensitivity analysis values ±50% of base-case value; # mortality rates used were age and sex specific, from the Australian Bureau of Statistics [54]; [c] Sensitivity analysis was carried out on total screening costs, not unit costs; [d] this estimate is based on expert opinion, as no cost data was available; [e] this estimate was based on production and dissemination costs from a large printing agency and Australia Post postage charges. GP refers to general practitioner

6.4.3 Interventions

Adults

Four screening interventions were modelled that reflect current practice, literature and available technology. All interventions were subject to variable uptake and adherence rates (Table 2), and all adult strategies were assumed to be performed through initial contact with a general practitioner (GP).

Strategy 1

Strategy 1 was based on the *status quo* approach in Australia. Current guidelines recommend screening either through a cascade approach in which first-degree relatives of a C282Y homozygote are offered concurrent genotyping and iron studies, or through incidental screening. This latter approach consists of three stages: two consecutive elevated TfS results followed by *HFE* genotyping. In our model, when a participant tested positive as a C282Y homozygote with either strategy, they moved into Markov states Category 1 or Category 2. For a patient who tested negative for C282Y homozygosity and had elevated transferrin saturation, a consultation with a specialist medical practitioner for further investigations was assumed. Apart from the cost of this consultation, no other consequences were considered.

Strategy 2

The second strategy was a population-based approach to screening, in that all 30 year old males and 45 year old females of northern European ancestry were offered *HFE* genotyping via a blood sample. Following a positive result, iron studies were conducted with a follow-up appointment with a GP.

Strategy 3

This strategy entailed *HFE* genotyping via a buccal cell sample obtained through a painless cheek-brush procedure. The benefits of this approach are that it is non-invasive, and in laboratory and screening studies, has been shown to have high sensitivity and specificity [40-43]. This strategy replicated Strategy 2 with the exception that instead of a blood sample for genotyping, a buccal cell sample was used.

Strategy 4

The fourth strategy was based in part on the *status quo*. Screening was assumed to be offered to all adults of northern European ancestry, and consisted of two consecutive iron studies, specifically TfS, which if elevated, were followed by a confirmatory *HFE* genotype.

Neonates

Strategy 5

The neonatal screening intervention involved *HFE* genotyping as an add-on to the existing newborn screening program [44]. Following birth, all neonates, irrespective of ancestry, were assumed to be offered genetic screening for a range of disorders, including haemochromatosis. This screening strategy assumed that 50% of adult C282Y homozygotes (males aged 30 and females aged 45 years) would have iron studies conducted with a GP and commence treatment if required. As neonates from all ancestries were included, a lower prevalence rate of 0.39% was adopted [45].

Strategy 6

The comparator for this strategy was the *status quo* (i.e. Strategy 1 for adult screening strategies), however, participants were simulated from birth. At age 30 for males and 45 for females, the screening approaches and assumptions described for Strategy 1 commenced.

6.4.4 Estimates of screening uptake

As no data on uptake of cascade and incidental screening in Australia were available, an estimate was made based on values used in other studies and expert opinion, and these estimates were thoroughly tested in univariate sensitivity analysis. The probability of being screened was set at 0.05 [45], and a probability of 0.5 was used for screening via cascade and incidental approaches respectively.

Similarly, as no population screening programs for haemochromatosis have been introduced internationally, an uptake rate was estimated. Uptake rates of two Australian screening programs were identified (bowel cancer screening: 36.0% [46] and cervical cancer: 57.8%[47]), and a mean of 0.469 was calculated and varied in sensitivity analyses by ±50%.

For neonatal screening, as this is close to being universal in Australia, the probability of uptake was assumed to be 1.0 [48-50]. The probability of having iron studies conducted as an adult was set at 0.5, based on expert opinion. To reflect the uncertainty around the estimate, this was varied by ±50% in one-way sensitivity analyses.

6.4.5 Adherence to treatment

The probabilities of adherence to treatment were taken from a longitudinal study following haemochromatosis patients over a nine year period [51]. From a baseline adherence rate of 90.5%, an annual linear decrease of 6.8% was reported. For our model, the probability of adherence in years 10+ plateaued at 29.3% (Table 2).

6.4.6 Sensitivity and specificity of screening tests

The model incorporated sensitivity and specificity estimates for the two consecutive TfS tests based on sex, and for *HFE* genotyping (Table 2). These estimates, in combination with prevalence estimates, were built into the model using Bayes' revision function, as detailed in our accompanying paper.

6.4.7 Costs

As the Australian Government would be the potential payer of a population screening program, the perspective of the government was taken. Total government costs included direct medical costs and transfer payments, with both reported separately. Transfer payments were included as they were found to contribute substantially to the overall costs associated with haemochromatosis [52]. All costs were reported in 2015 AUD (USD 0.75). Cost calculations and methodology have been reported in detail elsewhere [52], however a brief description is provided here .

Direct medical costs included medical consultations, procedures, investigations, prescribed medications and public hospital admissions. Costs were taken from the 2015 Medical Benefits Scheme (MBS), Pharmaceutical Benefits Scheme (PBS) and the National Hospital Cost Data Collection cost weights for Australian Refined Diagnosis-Related Group (AR-DRG) [53-55]. No cost data were available for *HFE*-genotyping with buccal swabs, so estimates were based on comparable investigations. Unit costs are displayed in Table 2. All costs associated with EASL

haemochromatosis disease states were sourced from our recently published cost of illness study (Table 2) [52].

Transfer payments, in the form of government welfare (Disability Support Pension, Carer's Allowance) were costed based on patients' and carers' reports from our cost of illness study [52].

As recommended by the Australian Medical Services Advisory Committee, costs and effectiveness were discounted by 5% annually [56]. The model was validated following the recommendations of the International Society of Pharmacoeconomics and Outcomes Research Task-Force 7 [57], described in detail in our accompanying paper [30].

6.4.8 Effectiveness

QALYs were used as a measure of effectiveness. Utility values for each category of disease severity were sourced from a recently published study [22]. QALYs were calculated by adjusting the time spent in a health state by the utility score assigned to that state.

6.4.9 Sensitivity analyses

Tornado diagrams were produced for each strategy, by sex for total government costs. These were used to identify the parameters with the greatest impact on outcomes when varied through plausible ranges. Prevalence, adherence to treatment, transition probabilities, utility values, the Category 4 mortality multiplier and costs were varied by ±20% of the values used in the base-case analyses [58]. For all model parameters that were informed by expert opinion, the estimates were varied ±50%, reflecting the greater uncertainty around these estimates. [58]. Discounting of costs and effectiveness was varied from zero to 7%. For variables that were defined by a distribution, probabilistic sensitivity analysis was conducted to incorporate multiple parameter uncertainties simultaneously.

6.5 Results

6.5.1 Adult strategies

Males

From the government perspective (direct medical costs and transfer payments) all three screening strategies were cost effective compared to the *status quo* (Table 3). The most cost-effective approach was genotyping (blood), which produced an ICER of AUD1,673/QALY gained, followed by the TfS strategy (AUD4,103/QALY gained) and genotyping (buccal) (AUD15,233/QALY gained). To address uncertainty, cost-effectiveness acceptability curves (CEACs) were produced. Whilst a willingness to pay (WTP) threshold has not been explicitly specified for the Australian context, an implicit threshold of AUD50,000/QALY gained is commonly used [59, 60]. In comparison with the *status quo*, the probability of genotyping (blood) being cost-effective at a WTP of AUD50,000 was 82%, for TfS screening 81%, and for genotyping (buccal) 74% (Figures 2a, c and b respectively). Ranking of the comparative cost-effectiveness of all strategies showed genotyping (blood) to be the dominant strategy (Table 4).

Similarly, when the analysis was limited to direct medical costs, all strategies for males were cost-effective when compared with the *status quo* (Table 3). The most cost-effective approach was genotyping (blood), with an ICER of AUD1,810/QALY gained, followed by TfS screening (AUD4,225/QALY gained) and genotyping (buccal) (AUD15,371/QALY gained). All three strategies returned ICERs below this threshold.

Females

All three screening strategies for females incurred greater costs than the *status quo.* For both genotyping strategies, the incremental gains in effectiveness were marginal (i.e. <0.001QALY), resulting in ICERs of AUD552,964 for genotyping (blood) and AUD1,872,055/QALY gained for genotyping (buccal). The incremental gain in effectiveness related to the TfS strategy was 0.002QALY, producing an ICER of AUD10,195/QALY gained. Applying the WTP threshold of AUD50,000, only the TfS strategy was considered to be cost-effective. The CEAC showed a 61% probability of this strategy being cost-effective with this WTP threshold (Figure 2f).

Ranking of the comparative cost-effectiveness for all strategies showed TfS to be the dominant strategy (Table 4).

When the analysis was limited to direct medical costs, similar results were produced (Table 3). For both genotyping strategies, ICERs of AUD559,675 for genotyping (blood) and AUD1,887,171/QALY gained for genotyping (buccal) were produced. The ICER associated with the TfS strategy was AUD10,253/QALY gained, below the WTP threshold of AUD50,000.

6.5.2 Neonatal strategies

Neonatal screening of both males and females resulted in cost savings and increased effectiveness, thereby dominating the *status quo* (Table 3). For males, the estimated cost savings associated with neonatal screening were AUD8 (6) and the incremental gain in effectiveness was 0.07 (0.020) QALY. For females, the cost savings associated with screening were AUD2 (2) and the incremental gain in effectiveness was 0.06 (0.02) QALY. Applying the WTP threshold, there was a 100% probability for both males and females that this strategy would be cost-effective (Figures 2g and 2h respectively). These results were unchanged when the analysis was limited to direct medical costs.

Table 3: Results of base-case cost effectiveness analyses: *status quo* vs alternate strategies for direct medical, transfer and total government costs

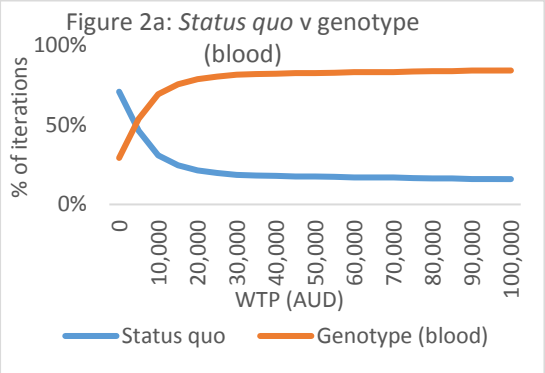
	Cost (SD)	Incremental cost (SD)	Effectiveness (QALY) (SD)	Incremental effectiveness (SD)	ICER ($/QALY gained)
Direct medical costs					
Adult males					
Status quo	145 (149)	-	15.654 (4.062)	-	-
Genotype screening (blood)	152 (99)	7 (55)	15.658 (4.062)	0.004 (0.004)	1,810
Genotype screening (buccal)	208 (99)	63 (55)	15.658 (4.062)	0.004 (0.004)	15,371
Transferrin saturation	160 (110)	15 (44)	15.657 (4.060)	0.003 (0.004)	4,225
Adult females					
Status quo	91 (135)	-	14.290 (3.955)	--	-
Genotype screening (blood)	115 (88)	24 (52)	14.390 (3.955)	<0.001 (0.005)	559,675
Genotype screening (buccal)	170 (89)	79 (52)	14.390 (3.955)	<0.001 (0.005)	1,887,171
Transferrin saturation	108 (101)	17 (35)	14.392 (3.958)	0.002 (0.005)	10,253
Neonate males					
Status quo	17.3 (11.2)	-	16.830 (4.386)	-	-
Genetic screen	9.5 (6.1)	-7.8 (5.5)	16.900 (4.406)	0.070 (0.020)	DOMINANT
Neonate females					
Status quo	5.3 (3.8)	-	16.667 (4.619)	-	-
Genetic screen	3.4 (2.2)	-1.9 (1.8)	16.723 (4.619)	0.055 (0.016)	DOMINANT
Transfer payments					
Adult males					
Status quo	1.8 (23.1)	-			
Genotype screening (blood)	1.2 (14.5)	-0.6 (8.7)			
Genotype screening (buccal)	1.2 (14.5)	-0.6 (8.7)			
Transferrin saturation	1.3 (16.2)	-0.4 (7.1)			

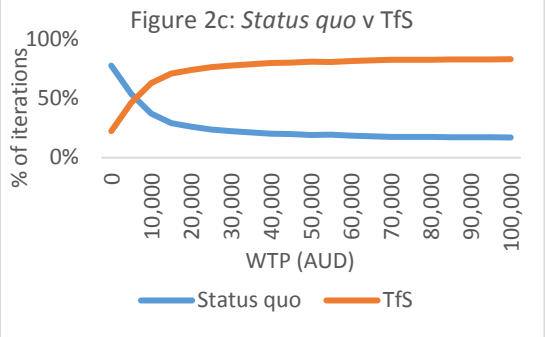
Adult females					
Status quo	0.4 (5.6)	-			
Genotype screening (blood)	0.3 (3.5)	-0.1 (2.2)			
Genotype screening (buccal)	0.3 (3.5)	-0.1 (2.2)			
Transferrin saturation	0.3 (4.1)	-0.1 (1.6)			
Neonate males					
Status quo	0.2 (1.4)	-			
Genetic screen	<0.01 (0.7)	-<0.01 (0.8)			
Neonate females					
Status quo	<0.1 (0.1)	-			
Genetic screen	<0.1 (<0.1)	-<0.1 (<0.1)			
Total government costs	Cost (SD)	Incremental cost (SD)	Effectiveness (QALY) (SD)	Incremental effectiveness (SD)	ICER ($/QALY gained)
Adult males					
Status quo	146 (151)	-	15.654 (4.062)	-	-
Genotype screening (blood)	153 (100)	7 (56)	15.658 (4.062)	0.004 (0.004)	1,673
Genotype screening (buccal)	209 (101)	63 (56)	15.658 (4.062)	0.004 (0.004)	15,233
Transferrin saturation	161 (111)	15 (45)	15.657 (4.060)	0.003 (0.004)	4,103
Adult females					
Status quo	92 (135)	-	14.390 (3.955)	--	-
Genotype screening (blood)	115 (89)	23 (52)	14.390 (3.955)	<0.001 (0.005)	552,964
Genotype screening (buccal)	171 (89)	79 (52)	14.390 (3.955)	<0.001 (0.005)	1,872,055
Transferrin saturation	109 (102)	17 (35)	14.392 (3.958)	0.002 (0.005)	10,195
Neonate males					
Status quo	17.5 (12.3)	-	16.830 (4.386)		-
Genetic screen	9.5 (6.1)	-7.9 (5.5)	16.900 (4.406)	0.070 (0.020)	DOMINANT
Neonate females					
Status quo	5.3 (3.8)	-	16.667 (4.602)	-	-
Genetic screen	3.4 (2.2)	-1.9 (1.7)	16.723 (4.619)	0.055 (0.016)	DOMINANT

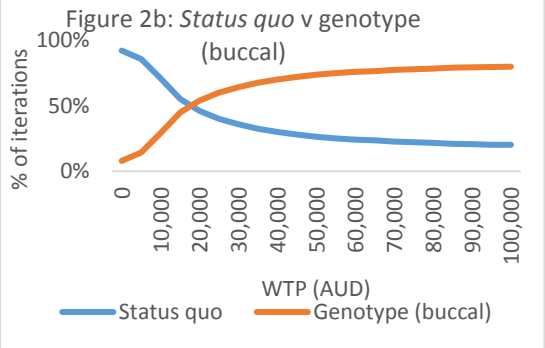
ICER Incremental cost effectiveness ratio; QALY quality adjusted life year. Note: all costs are reported in 2015 AUD

Figure 2: Cost-effectiveness acceptability curves, total government costs

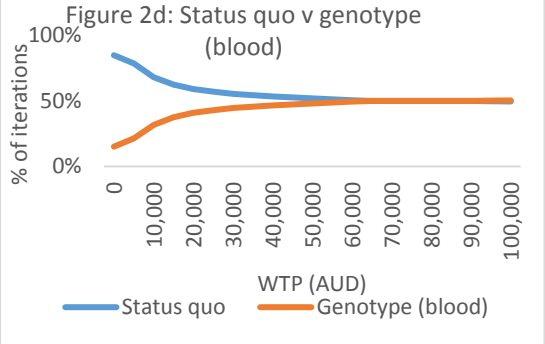
Male adults

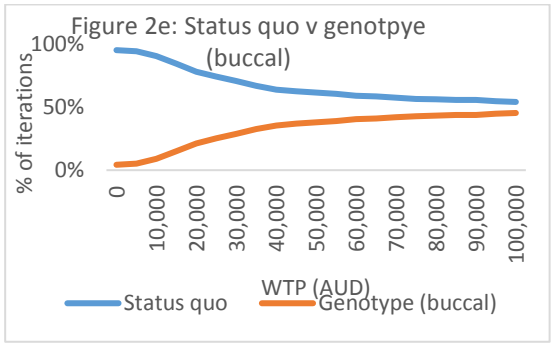


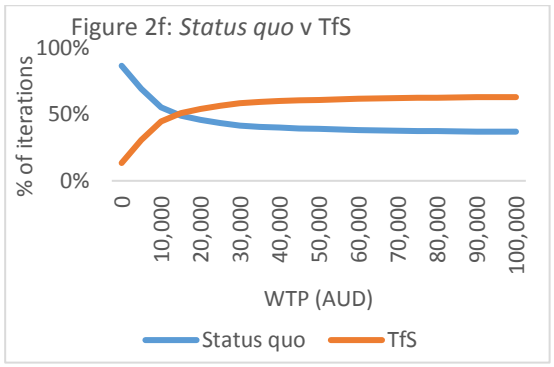




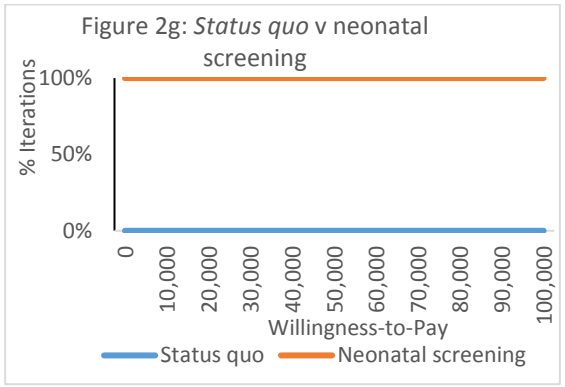
Female adults







Male neonates



Female neonates

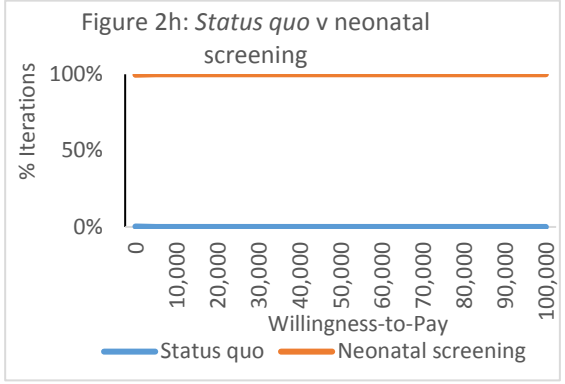


Table 4: Rankings of cost-effectiveness, excluded dominated strategies

Strategies*	Cost	QALYs gained	ICER
Male adults:			
Genotype screening (blood)	153	15.658	DOMINANT
Genotype screening (buccal)	209	15.658	WEAKLY DOMINATED
Status quo	146	15.654	WEAKLY DOMINATED
Female adults:			
Transferrin saturation	109	14.392	DOMINANT
Status quo	92	14.390	WEAKLY DOMINATED

* Strategies that were strongly dominated were excluded.

6.5.3 Cases identified

The number of cases identified (true positives) per 10,000 screenings was calculated for each strategy (Table 5). For the *status quo*, the model projected 2.88 male and 2.03 female homozygotes would be identified. For adult strategies, both genotype strategies (blood and buccal) were the most effective, identifying 26.64 cases for males and females respectively. Population screening using TfS was similarly efficient for males, identifying 24.68 cases, however for females only 8.78 cases were identified. The lower sensitivity of TfS for identifying female homozygotes was the driver for this difference.

For the neonatal screening strategy, a lower prevalence rate of 0.0039 was adopted, reflecting screening irrespective of ancestry [45]. The model estimated that 35.86 male and female homozygotes respectively would be identified, notably higher than the *status quo.*

Table 5: Number of C282Y homozygotes identified per 10,000 screenings

	Male	Female
Adult strategies:		
Status quo	2.88	2.03
Genotype screening (blood)	26.64	26.64
Genotype screening (buccal)	26.64	26.64
Transferrin saturation	24.68	8.78
Neonatal strategies:		
Status quo	2.88	2.03
Genetic screen	35.86	35.86

6.5.4 Sensitivity analysis

One-way sensitivity analysis for each parameter that contributed moderate to large variations identified in the tornado diagrams was carried out for total government costs (Appendix 6A). Parameters were varied ±20%, with the exception of screening uptake and uptake of iron studies in homozygote adults screened as neonates (±50%), and the discount rate (0 and 7%).

Adult males

For males, the base-case analysis for genotype (blood) screening produced an ICER of AUD1,673/QALY gained. This strategy dominated the *status quo* in all one-way sensitivity analyses, with the exception of increasing the discount rate to 7%, which produced an ICER of AUD2,674/QALY gained.

In the base-case analysis for genotyping (buccal) males, an ICER of AUD15,233/QALY gained was calculated. Decreasing the discount rate to zero resulted in this strategy dominating the *status quo.* All other sensitivity analyses produced ICERs ranging between AUD6,139 and 23,882/QALY gained.

Screening with TfS produced an ICER of AUD4,103/QALY gained in the base-case analysis. This strategy was found to dominate the *status quo* when the discount rate was decreased to zero, baseline age for screening was decreased to 20 years, the probability of starting in Category 1 was decreased (thereby increasing penetrance), increasing the prevalence estimate and increasing the probability of transition from Category 1 to 2 (in the absence of treatment). All other sensitivity analyses produced ICERs ranging between AUD41 and 5,910/QALY gained.

Adult females

In the base-case analysis, genotyping (blood) produced an ICER of AUD552,964/QALY gained. Reducing the discount rate to zero resulted in this becoming a dominant strategy, however this strategy was dominated by the *status quo* when the discount rate was increased to 7%, baseline age for screening was raised to 55 years, prevalence was increased and the transition probability of moving between Categories 2 and 3 (in the absence of treatment) was decreased. All other sensitivity analyses produced ICERs above the AUD50,000 WTP threshold, ranging between AUD84,605 and 1,245,111/QALY gained.

The base-case analysis for genotyping (buccal) females had an ICER of AUD1,872,055/QALY gained. Reducing the discount rate to zero produced an ICER of AUD13,227/QALY gained, however all other sensitivity analyses resulted in this strategy being dominated by the *status quo* or producing ICERs well above the WTP threshold, ranging between AUD331,102 and 4,315,313/QALY gained.

Screening with TfS returned an ICER of AUD10,195/QALY gained in the base-case analysis. Whilst reducing the discount rate to zero resulted in this strategy dominating the *status quo,* all other sensitivity analyses produced ICERs ranging between AUD797 and 17,500/QALY gained.

Neonatal screening

One-way sensitivity analyses showed little effect on the base-case results, with neonatal screening dominating the *status quo* in all analyses for both sexes. In particular, assumptions regarding the uptake of screening and iron studies in homozygote adults (screened as neonates) – which were based on expert opinion – had little impact on the base-case results.

6.6 Discussion

This is the first haemochromatosis screening model to incorporate utilities and costs derived from a haemochromatosis cohort. A Markov model with probabilistic decision analysis was developed to estimate the cost-effectiveness of screening both adults and neonates in Australia .To date, just one other study has used these methods, which was based on a hypothetical population of 30 year old German males [37]. We have built on this study by using QALYs rather than LYG as the measure of effectiveness, and including females and neonates.

All three screening strategies were cost-effective for adult males in the base-case and sensitivity analyses. Applying a WTP threshold of AUD50,000/QALY gained, the probability that each strategy would be cost-effective ranged between 74% and 82%. For adult females, screening with TfS was the only strategy found to be cost-effective; applying the WTP threshold, there was a 61% probability of this strategy being cost-effective.

These results differ from a recent screening study for German males from the payer perspective [37], in which three screening strategies were compared with no screening for males aged 30 in a Markov model using probabilistic sensitivity analysis. Sequential population screening (similar to our TfS screening) was reported to have an ICER €124,000/LYG and genotype population screening (similar to our genotyping with a blood sample) had an ICER of €161,000/LYG. In contrast, from the government perspective, our study estimated an ICER of AUD4,225/QALY gained for the TfS strategy and 1,810/QALY gained for genotype screening (blood). There are several reasons for these contrasting results. Firstly, different measures of effectiveness were used: LYG and QALYs. Use of QALYs allowed for inclusion of a broad range of quality of life impacts related to haemochromatosis [21, 22]. Therefore, it is not surprising that our study shows more favourable results for population screening as we used a more comprehensive definition of effectiveness that captured effects of screening on both length and quality of life. Secondly, the German study limited its state costs to those related to cirrhosis and hepatocellular carcinoma; we included a broad range of complications as outlined in the EASL categories (Table 1). As a result, our model captured a broader range of costs.

Genotyping with buccal cell samples was the least favourable option, due to the relatively high cost of this test. As genotyping with buccal samples is not routinely performed in Australia (in favour of blood samples) the economies of scale associated with this have resulted in lower comparative costs for genotyping with blood samples rather than buccal samples. As buccal samples represent a non-invasive approach with comparable sensitivity and specificity to blood samples, this may change over the coming decade. If this occurs, then it is possible that genotyping with buccal samples will become more favourable from a cost-effectiveness perspective.

The model was sensitive to the discount rate as it was applied annually to both costs and effectiveness which were projected over a long time horizon, thereby impacting on costs and QALYs accrued in the future. In the modelled scenarios, immediate costs of screening were offset by long-term reductions in costs associated with progression of the severity of disease. Similarly, improvements in QALYs accrued in the future due to reduced progression of disease severity were reduced due to discounting. While varying the discount rate had a large impact

on the absolute costs and QALYs calculated for each scenario, as would be expected in a lifetime analysis, the decision as to whether or not the interventions were deemed to be cost-effective (i.e. fall under the Australian willingness to pay threshold of $50,000) did not change.

Neonatal screening dominated the *status quo* for males and females. This appears to be an excellent prospect for screening from a cost-effectiveness viewpoint, and avoids exclusion from screening based on ancestry. However, establishing cost-effectiveness is just one of many elements when considering instituting population screening programs [61]. The current Australian guidelines for neonatal screening specify that screened conditions be limited to those that should be identified early in life to minimise morbidity or mortality. As haemochromatosis does not meet this criterion, *HFE* genotyping is unlikely to be included in neonatal screening protocols at present. Secondly, the issue of how an adult who, as a neonate tested positive for the screening test, would be alerted of this status as an adult, is unclear. We did not consider this in our model, however, it is possible that national genetic registry programs may be established in the future, which would co-ordinate follow-up of individuals carrying genetic mutations that elevate disease risks.

The adult model predicted that for 10,000 screenings, the *status quo* would identify an estimated 2.88 and 2.03 male and female homozygotes respectively. Using the prevalence estimate of 0.68% for people of northern European ancestry [6], from a population of 10,000 people of such ancestry, 68 would be expected to be C282Y homozygotes. This suggests that the current approach to screening in Australia is of limited efficiency, identifying approximately 3% of C282Y homozygotes. In comparison, our model estimated approximately 40% of homozygotes would be identified through our adult screening approaches (with the exception of TfS screening for females), and 92% of neonates. The potential inefficiency of the current approach suggests that alternatives should be considered, such as those included in our model, which would identify a greater proportion of C282Y homozygotes. Increasing the rate of diagnosis and treatment of iron overload will likely to lead to reduced costs [52] and importantly, reduced morbidity and mortality [62].

An important limitation to the results obtained through our analyses are the uncertainties represented by large standard deviations for costs and effectiveness. This is predominantly

due to the dispersion of data in the source studies [22, 52]. The fact that one-way sensitivity analyses had limited effect on most base-case results (with the exception of discounting), and the CEACs showed high probabilities that most strategies were likely to be cost-effective, suggests that the results generated by the model are robust nevertheless. A further limitation was the unavoidable reliance on expert opinion. Whilst this was addressed by conducting one-way sensitivity analyses on these estimates, more robust estimates would strengthen future models.

There are several strengths of this model. We used probabilistic decision analysis in a Markov model, which allowed for multiple parameter uncertainties to be accounted for in the analyses. Use of QALYs allowed for quality of life impacts to be incorporated rather than limiting the focus to mortality. This is the first economic analysis of haemochromatosis screening to include comprehensive haemochromatosis-specific costs and utilities. Finally, this is the first model to incorporate costs associated with transfer payments.

We have developed a comprehensive economic model to examine the cost-effectiveness of screening both adults and neonates for haemochromatosis in Australia. The results of this model suggest that screening males of northern European ancestry aged 30years with genotyping using blood samples is likely to be a cost-effective strategy. For females, screening with TfS was the most favourable strategy. Neonatal screening was associated with cost savings and improved effectiveness in comparison to the *status quo*. These results may assist decision-makers when considering the implementation of haemochromatosis screening programs in Australia.

6.7 References

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Appendix 6A: Sensitivity analyses

	Mean costs				Mean effectiveness				ICER (AUD/QALY gained)		
Model parameters	*Status quo*	Genotype (blood)	Genotype (buccal)	TfS	*Status quo*	Genotype (blood)	Genotype (buccal)	TfS	Genotype (blood)	Genotype (buccal)	TfS
TOTAL GOVERNMENT COSTS											
Adult males											
Discount rate: 0%	739	582	637	651	42.246	42.264	42.264	42.262	DOMINANT	DOMINANT	DOMINANT
Discount rate: 7%	132	139	195	146	11.903	11.906	11.906	11.905	2,674	23,882	5,910
Baseline age: 20 years	211	196	252	208	16.051	16.056	16.056	16.055	DOMINANT	9,263	DOMINANT
Baseline age: 40 years	170	168	223	178	14.528	14.531	14.531	14.531	DOMINANT	14,594	2,379
Prevalence: -20%	171	166	222	183	15.453	15.457	15.457	15.456	DOMINANT	14,279	3,458
Prevalence: +20%	252	229	285	228	15.451	15.456	15.456	15.455	DOMINANT	6,139	DOMINANT
Probability of starting in category 1: -20%	216	196	252	209	15.451	15.456	15.456	15.455	DOMINANT	7,646	DOMINANT
Probability of starting in category 1: +20%	172	171	227	182	15.454	15.457	15.457	15.457	DOMINANT	16,167	3,701
Transition from category 1 to 2~: -20%	180	173	229	184	15.453	15.457	15.457	15.457	DOMINANT	12,876	1,257
Transition from category 1 to 2~: +20%	205	193	248	205	15.452	15.456	15.456	15.455	DOMINANT	10,171	DOMINANT
Transition from category 2 to 3~: -20%	184	177	233	188	15.454	15.457	15.457	15.457	DOMINANT	12,996	1,105
Transition from category 2 to 3~: +20%	202	190	245	202	15.452	15.456	15.456	15.455	DOMINANT	10,077	41
Category 4 mortality: -20%	195	185	240	196	15.453	15.457	15.457	15.456	DOMINANT	11,210	124
Category 4 mortality: +20%	193	183	239	195	15.452	15.457	15.457	15.456	DOMINANT	11,281	749
Uptake of screening: -50%	194	188	216	195	15.452	15.454	15.454	15.454	DOMINANT	11,871	1,030
Uptake of screening: +50%	194	180	263	196	15.453	15.459	15.459	15.458	DOMINANT	11,059	293
Adult females											
Discount rate: 0%	313	279	334	284	33.124	33.126	33.126	33.129	DOMINANT	13,227	DOMINANT
Discount rate: 7%	71	99	154	93	11.286	11.286	11.286	11.287	DOMINATED	DOMINATED	16,726
Baseline age: 35 years	115	131	186	127	15.243	15.243	15.243	15.245	89,955	412,446	5,967

Baseline age: 55 years	82	108	163	101	12.865	12.865	12.865	12.866	DOMINATED	DOMINATED	13,330
Prevalence: -20%	89	111	166	109	14.281	14.281	14.281	14.283	244,675	877,007	17,500
Prevalence: +20%	129	146	201	132	14.277	14.277	14.277	14.280	DOMINATED	DOMINATED	797
Probability of starting in category 1: -20%	122	132	188	128	14.280	14.280	14.280	14.282	123,766	765,431	3,401
Probability of starting in category 1: +20%	95	117	173	112	14.280	14.280	14.280	14.282	1,245,111	4,315,313	10,304
Transition from category 2 to 3~: -20%	97	118	174	113	14.281	14.280	14.280	14.282	DOMINATED	DOMINATED	10,087
Transition from category 2 to 3~: +20%	103	122	178	118	14.280	14.280	14.280	14.281	84,605	331,102	7,795
Category 4 mortality: -20%	101	121	176	116	14.280	14.280	14.280	14.282	679,294	2,566,244	8,693
Category 4 mortality: +20%	100	120	176	115	14.280	14.280	14.280	14.282	578,325	2,174,662	8,898
Uptake of screening: -50%	99	109	136	107	14.280	14.280	14.280	14.281	620,125	2,336,773	9,264
Uptake of screening: +50%	102	132	216	124	14.280	14.280	14.280	14.283	620,125	2,336,773	8,649

	Mean costs		Mean effectiveness		ICER (AUD/QALY gained)
	Status quo	Neonatal screening	*Status quo*	Neonatal screening	Neonatal Screening
Neonatal males					
Discount rate: 0%	292	138	65.837	66.257	DOMINANT
Discount rate: 7%	8	5	12.316	12.367	DOMINANT
Prevalence: -20%	18	9	16.612	16.681	DOMINANT
Prevalence: +20%	26	13	16.613	16.681	DOMINANT
Probability of starting in category 1: -20%	23	12	16.612	16.681	DOMINANT
Probability of starting in category 1: +20%	18	10	16.613	16.681	DOMINANT
Transition from category 1 to 2~: -20%	19	10	16.613	16.681	DOMINANT
Transition from category 1 to 2~: +20%	22	12	16.612	16.681	DOMINANT
Transition from category 2 to 3~: -20%	19	10	16.613	16.681	DOMINANT
Transition from category 2 to 3~: +20%	21	11	16.612	16.681	DOMINANT
Category 4 mortality: -20%	20	11	16.612	16.681	DOMINANT
Category 4 mortality: +20%	20	11	16.612	16.681	DOMINANT
Uptake of Fe screening for HMZ: -50%	20	11	16.612	16.681	DOMINANT
Uptake of Fe screening for HMZ: +50%	20	11	16.612	16.681	DOMINANT

Uptake of *status quo* screening*:* -20%	20	11	16.613	16.491	DOMINANT
Uptake of *status quo* screening*:* +20%	21	11	16.612	16.981	DOMINANT
Neonatal females					
Discount rate: 0%	120	62	68.497	68.853	DOMINANT
Discount rate: 7%	2	2	12.221	12.261	DOMINANT
Prevalence: -20%	5	3	16.540	16.595	DOMINANT
Prevalence: +20%	7	4	16.539	16.594	DOMINANT
Cost of neonatal screen: -20%	5	3	16.540	16.594	DOMINANT
Cost pf neonatal screen: +20%	5	4	16.540	16.594	DOMINANT
Probability of starting in category 1: -20%	6	4	16.540	16.594	DOMINANT
Probability of starting in category 1: +20%	5	3	16.540	16.594	DOMINANT
Transition from category 1 to 2˜: -20%	5	3	16.540	16.594	DOMINANT
Transition from category 1 to 2˜: +20%	6	4	16.540	16.594	DOMINANT
Transition from category 2 to 3˜: -20%	5	3	16.540	16.594	DOMINANT
Transition from category 2 to 3˜: +20%	6	4	16.540	16.594	DOMINANT
Category 4 mortality: -20%	5	3	16.540	16.594	DOMINANT
Category 4 mortality: +20%	5	3	16.540	16.594	DOMINANT
Uptake of Fe screening for HMZ: -50%	5	3	16.540	16.594	DOMINANT
Uptake of Fe screening for HMZ: +50%	5	4	16.540	16.594	DOMINANT
Uptake of *status quo* screening*:* -20%	5	3	16.540	16.594	DOMINANT
Uptake of *status quo* screening*:* +20%	6	3	16.540	16.594	DOMINANT

* All ICERs are calculated against the s*tatus quo*; ˜ Refers to transitions where no treatment was included

Chapter 7: Summary and future directions

7.1 Preface

This thesis presented an overview of the current status of the global health economic evidence for haemochromatosis screening and interventions, estimates the economic and health-related quality of life burden associated with haemochromatosis for the Australian setting, and identifies cost-effective population screening strategies. This chapter provides a synopsis, discussion and suggestions for future directions.

7.2 Summary of the thesis

Chapter 1 provided an overview of haemochromatosis and health economics. One of the most common genetic disorders amongst populations of northern European heritage [1, 2], haemochromatosis is largely straightforward to both diagnose and treat. However, as early symptoms are non-specific and therefore easily missed, diagnosis is delayed in some cases, leading to preventable morbidity and mortality [3, 4]. Population screening programs have been suggested to increase early diagnosis and treatment, thereby reducing the associated burden of disease [5-8]. To date, a paucity of robust health economic evidence has been a key barrier to establishing such programs internationally [5, 9-11]. For governments, who are frequently the funding body for screening programs, provision of such interventions incur substantial costs. Therefore, it is important to conduct health economic evaluations to assess the value-for-money of clinically effective screening strategies. Modelling provides an excellent method to quantify the costs and effectiveness associated with proposed screening strategies, to inform decision makers when considering funding screening programs [12].

A systematic review of the global health economic literature pertaining to haemochromatosis was provided in Chapter 2. This review identified 38 published papers containing health economic data, most of which were modelled studies evaluating the cost-effectiveness of screening for haemochromatosis. Whilst the majority of studies concluded that screening for haemochromatosis was cost-effective, many included flawed assumptions or methodology,

limiting the validity of the results. The gaps identified in the systematic review regarding current knowledge and understanding of health economic aspects of haemochromatosis informed the direction of the subsequent PhD projects.

The review identified that to date, no study had reported on health-related quality of life associated with haemochromatosis, in the form of health state utility values (HSUVs). Four studies had incorporated HSUVs into their models, however, almost all were unrealistically high, likely resulting in underestimates of the effectiveness of screening. Secondly, no literature was identified that reported on the economic burden associated with haemochromatosis. Quantification of both the health-related quality of life impacts and economic burden associated with haemochromatosis would allow for greater understanding of its burden, and further, the effects a proposed population screening program may offer.

Chapter 3 presents a study on the health-related quality of life utility values for haemochromatosis. A national online survey was conducted, using the Assessment of Quality of Life 4D (AQOL-4D) instrument to elicit HSUVs. Participants were categorised into four stages of disease, as recommended by the European Association for the Study of the Liver [9], and described in Table 7.1. Mean utilities (standard deviation) were 0.76 (0.21) for Category 1, 0.81 (0.18) for Category 2, 0.60 (0.27) for Category 3, and 0.50 (0.27) for Category 4. The value for Category 4 was similar to those reported for comparable co-morbidities, such as liver cirrhosis and heart disease. Self-reported symptoms associated with iron overload were negatively associated with HSUV (r=-0.685). Previous health economic evaluations of haemochromatosis screening used unrealistically high HSUVs in most cases: 1.00 for all symptoms and co-morbidities with the exception of cirrhosis, which was assigned a utility of 0.95 [7]; 0.8 for cirrhosis, 0.9 for diabetes, 0.5 for heart failure [13, 14]. Use of inflated utilities in health economic analyses is likely to lead to underestimates of gains in effectiveness associated with an intervention. The utility values reported in this study, the most robust reported to date, can be used to populate future health economic models for haemochromatosis interventions.

Chapter 4 presents data on the economic burden associated with C282Y homozygous haemochromatosis in Australia, the first study to quantify this and to provide a breakdown of the effects of increasing severity of disease on costs. Through the national cost of illness study

estimates of health sector, other sector and time-loss/productivity costs from the perspectives of the patient, government and society were obtained. Per patient costs were estimated for each category of haemochromatosis. Costs from the societal perspective were then extrapolated to the Australian population for asymptomatic (Categories 1 and 2) and symptomatic patients (Categories 3 and 4) for both diagnosed and undiagnosed C282Y homozygotes. Whilst the costing methodology was based on previously described costing studies [15, 16], an additional novel approach was applied to allow for the estimation of costs for undiagnosed patients. This approach allowed for a more comprehensive estimation of total costs which is critical for a condition with a low diagnosis rate such as haemochromatosis. The total annual cost associated with C282Y homozygous haemochromatosis in Australia was estimated to be AUD274 million in 2015. Sensitivity analyses identified substantially lower costs associated with decreased penetrance of haemochromatosis. These cost estimates provide the first estimates of the economic burden associated with haemochromatosis internationally, and the estimates for each level of severity of disease can be used to populate future health economic models.

Chapters 5 and 6 focus on the health economic model that was developed to analyse the cost-effectiveness of different haemochromatosis screening strategies in Australia. Chapter 5 provides an overview of the construction and validation of the model, following the guidelines of the International Society for Pharmacoeconomics and Outcomes Research [17]. A Markov state-transition model with states based on disease severity was constructed. For the purposes of this paper, the model was limited to the *status quo* approach (cascade and incidental screening) for males aged 30 years and females aged 45 years, both of northern European ancestry. Costs were reported from the government perspective, and were limited to direct medical costs. The model was found to have good face validity, along with internal and external validity. The model predicted mean (95%CI) QALYS of 15.7 (7.7-23.7) for males and 14.4 (6.7-22.1) for females associated with the *status quo* approach. The mean (95% CI) discounted lifetime direct medical costs for C282Y homozygote were estimated to be AUD22,737 (3,670-75,793) for males and AUD13,840 (1,335-67,377) for females. One-way sensitivity analyses revealed that discount rates, prevalence and state probabilities were the most influential parameters, and the few parameters that by necessity were based on assumptions had little impact on the overall results.

Chapter 6, extending upon Chapter 5, presents the results of the model for adults (males aged 30 years and females aged 45 years) of northern European ancestry and neonates irrespective of ancestry (from birth) to enable the assessment of the cost-effectiveness of potential screening strategies against the status quo. Four adult screening strategies were modelled: the *status quo* (cascade and incidental screening), genotyping with blood samples, genotyping with buccal samples, and transferrin saturation followed by genotyping (TfS); and two neonatal strategies: genetic screening and the *status quo* from birth. Approximately 3% of C282Y homozygotes were estimated to be identified with the *status quo* approach, compared with 40% for most adult strategies and 92% for neonatal strategies. Cost-effectiveness was estimated from the government perspective, including direct medical costs and transfer payments. For adult males, the most cost-effective strategy was genotyping with a blood sample, producing an ICER of AUD1,673 per additional QALY gained; for females, the TfS strategy was the most cost-effective, with an ICER of AUD10,195 per additional QALY gained. Neonatal screening dominated the *status quo* for both males and females.

In summary, the work that has been presented in this thesis has substantially added to the haemochromatosis body of literature, and will be useful to researchers, clinicians and decision makers. Future directions in this field will now be discussed.

7.2.1 Integrated conclusions of the thesis

In Chapter 1, Wilson and Jungner's criteria for population screening were presented (Textbox 1) [18], with the observation that, with the exception of criterion point 9, haemochromatosis is a condition that meets these criteria [19]. The studies presented in this thesis have provided valuable health economic data to specifically address criterion point 9: hereditary haemochromatosis, particularly the more severe stages (i.e. Categories 3 and 4) is associated with reduced health state utility values (Chapter 3) and an increased economic burden (Chapter 4), and that several population screening strategies for haemochromatosis were estimated to be cost-effective or cost saving in comparison to the *status quo* (Chapter 6).

Over the preceding two decades, a body of literature has developed providing high quality evidence of the natural history, diagnostic and treatment approaches for haemochromatosis approaches. These data, in combination with the health economic data presented in this

thesis, provide a strong evidence base for consideration of a policy to introduce population screening for haemochromatosis in Australia.

Textbox 1: Wilson and Jungner's screening criteria [18]

1. The condition sought should be an important health problem;
2. There should be an accepted treatment for patients with recognized disease;
3. Facilities for diagnosis and treatment should be available;
4. There should be a recognizable latent or early symptomatic stage;
5. There should be a suitable test or examination;
6. The test should be acceptable to the population;
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood;
8. There should be an agreed policy on whom to treat as patients;
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole;
10. Case finding should be a continuing process and not a "once and for all" project.

7.3 Future directions

7.3.1 Incorporating males and females into one model

The health economic model that was constructed calculated the cost-effectiveness of screening interventions for males and females separately. This approach was adopted due to the sex-dependent penetrance rates and different ages of onset of iron overload, with males experiencing a greater burden of disease. To some degree, this approach reflected the current body of literature which has focused on the cost-effectiveness of screening males. The work included in this thesis has shown that for adult males, genotype screening with either blood or buccal cell samples are likely to be cost-effective strategies, however, for females only the sequential strategy was found to be cost-effective. In reality, a screening strategy for haemochromatosis is likely to be introduced irrespective of sex, therefore it is important to

further refine the model to allow for simulation of a cohort of both males and females, in order to calculate the overall cost-effectiveness of each of these strategies compared with the *status quo*. This information is considered essential for decision-makers.

In Australia, the Medical Services Advisory Committee (MSAC) of the Australian Government Department of Health is the key decision making body for funding decisions regarding national screening programs. An important next step in this work will be to support the national support group, Haemochromatosis Australia, in the preparation of an MSAC submission. Therefore, the model will be refined to meet the reporting requirements of this body. This work has recently commenced, and publication of the results of the model will follow.

7.3.2 Improving estimates of screening uptake

In the model described in this thesis, published literature and expert opinion were used to inform the estimate of uptake of the proposed screening strategies for adults, as no published data were available. The estimate was based on the uptake rates of two Australian population screening programs: bowel and cervical cancer. For neonatal screening, expert opinion was relied upon to estimate uptake of iron studies for adults who were screened as neonates and found to be C282Y homozygotes. Whilst sensitivity analyses of ±50% were conducted for these estimates to evaluate how variations in these estimates impact the base-case results, it is preferable to use estimates based on more relevant data. Ideally, such an estimate would be derived from an evaluation of a real-world population screening strategy. Whilst this is feasible for an adult screening strategy, for the neonatal strategy, a follow-up period of 45 years would be required to evaluate uptake of iron studies of C282Y homozygote females, which is unlikely to be considered viable.

7.3.3 Adapting the model to other settings

The cost-effectiveness model that was presented in this thesis was developed for Australia, based on the *status quo* approach to diagnosis and using country-specific cost and utility data. The model has been constructed to allow for adaptation to other settings. New strategies can be simulated, and the parameters of the existing strategies altered. Further, when country-specific cost and utility data become available, these can be easily incorporated into the model. This will provide decision makers with a robust estimate of the cost effectiveness of

screening strategies specific to the setting.

7.3.4 Determination of country-specific cost and health state utility data

To allow for the cost-effectiveness model to be adapted to other settings, country-specific cost and utility are required to produce the most robust and valid results [20]. To date, these data have only been published for Australia. For countries with high prevalence of haemochromatosis such as Ireland [21]and Sweden [22], these data could be collected and used to adapt and validate the model for these settings, thereby providing robust evaluations of the cost-effectiveness of screening.

7.3.5 Conducting a budget impact assessment

A budget impact analysis is an important element to be included in MSAC submissions. It provides estimates to the funding body of the likely costs of implementing and maintaining a new intervention such as population screening for haemochromatosis. This work will involve constructing a model to allow for estimation of the likely impact on the Australian health budget that a screening program would have. The model will incorporate the most robust epidemiological and economic data available, consistent with the cost-effectiveness model. This work is planned to be conducted as part of an Honours or Masters project at Menzies Institute for Medical Research under the supervision of members of the health economics group.

7.3.6 Collaborating with the Centres for Disease Control and Prevention (CDC) on a paper reviewing the quality of evidence used in haemochromatosis models

In February of 2015, BdG was invited by a senior health economist from the Centres for Disease Control and Prevention (CDC), Dr Scott Grosse, to assist in conducting a review of the quality of evidence that has been used to populate health economic models for haemochromatosis screening. This invitation was a result of the systematic review that was published which identified this issue. This work will begin by the end of 2016, with submission planned for 2017.

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Publication arising from this thesis

Chapter 2:

de Graaff, B., Neil, A., Sanderson K, Si, L., Yee, K.C. & Palmer AJ. "A Systematic Review and Narrative Synthesis of Health Economic Studies for Hereditary Haemochromatosis" *Applied Health Economics and Health Policy.* October 2015; 13(5): 469-83.

Chapter 3:

de Graaff, B., Neil, A., Sanderson, K., Yee, K.C. & Palmer AJ. "Quality of life utility values for hereditary haemochromatosis in Australia" *Health and Quality of Life Outcomes*. February 2016; 14(31).

Chapter 4:

de Graaff, B., Neil, A. Sanderson K, Yee, K.C. & Palmer AJ. "Costs associated with hereditary haemochromatosis in Australia: A cost of illness study" *Australian Health Review*: Accepted for publication.

Chapter 5:

de Graaff, B., Lei, S., Neil, A., Yee, K.C., Sanderson, K., Gurrin, L.C. & Palmer AJ. **"**Population screening for hereditary haemochromatosis in Australia: construction and validation of a state-transition cost-effectiveness model" This manuscript has been submitted to *Applied Health Economics and Health Policy*.

Chapter 6:

de Graaff, B., Neil, A., Lei, S., Yee, K.C., Sanderson, K., Gurrin, L.C. & Palmer AJ. "Cost-effectiveness of different population screening strategies for hereditary haemochromatosis in Australia" This manuscript has been submitted to *Applied Health Economics and Health Policy*.

Other publications

Si, L., Winzenberg, TM., de Graaff, B. & Palmer, AJ. (2014) A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. *Osteoporosis International.* 25(8) pp.1987-97.

Neil, A. & **de Graaff, B**. (2016) Need, want and demand: What is really happening with low-acuity presentations. *Emergency Medicine Australasia* (DOI: 10.1111/1742-6723.12591).

Conference presentations arising from this thesis

Oral presentations

2014 Australasian Haemochromatosis Conference, Melbourne 2014, invited speaker

"*Screening for Hereditary Haemochromatosis: economic evaluations in the Australian setting"* 18 May

2014 Haemochromatosis Australia Annual General Meeting, Hobart 2014, invited speaker

"*Screening for Hereditary Haemochromatosis: economic evaluations in the Australian setting"* 9 August

2015 Australian Health Economics Society Doctoral (AHED) workshop, Brisbane

"Quality of life utility values for hereditary haemochromatosis" 30 September

2015 Australian Health Economics Society (AHES) Conference, Brisbane

"*Costs of hereditary haemochromatosis: An Australian cost of illness study"* 1 October

2016 Australasian Haemochromatosis Conference, Brisbane: invited plenary speaker

"*The Cost-Effectiveness of Screening for Haemochromatosis in Australia"* 6 August

"The societal costs associated with hereditary haemochromatosis in Australia" 6 August

2016 Australian Health Economics Society Conference (AHES), Perth.

"Screening for haemochromatosis in Australia: results of health economic modelling" 26 September.

Poster presentations

2013 University of Tasmania Higher Degree Research Conference
"The Health Economics of Screening for Hereditary Haemochromatosis in Australia" July 1

2015 International Society for Pharmacoeconomics and Outcomes Research, Philadelphia

"*The Impact of Increasing Severity of Hereditary Haemochromatosis on Quality of Life Utility Values"* 20 May

2016 International Society for Pharmacoeconomics and Outcomes Research, Singapore "*Cost-effectiveness of population screening for haemochromatosis in Australia: a state-transition model"* 5 August

2016 International Society for Pharmacoeconomics and Outcomes Research, Singapore "*An Australian national cost of illness study for hereditary haemochromatosis"* 5 August

Awards received

2014 University of Tasmania Vice Chancellor's Leadership Award

2015 Student travel grant, International Society for Pharmacoeconomics and Outcomes Research 20th International Conference, Philadelphia, USA.

2015 Selectively chosen to participate in the 3rd Australian Health Economics Society Doctoral workshop, Perth Australia (second place).